zugt in weniger als 30 s nach Applikation im Mundraum zerfällt.

19. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer schnell im Mundraum zerfällt, der Wirkstoff aber an einen Ionentauscher gebunden bleibt, der den Wirkstoff erst im Gastrointestinaltrakt freisetzt.

20. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Wirkstoffe in diskreten Schichten enthalten sind, die räumlich voneinander getrennt sind und sich in ihrem Aufbau voneinander unterscheiden.

21. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung als Schaum vorliegt und mindestens einer der Wirkstoffe in flüssiger Form in den Hohlräumen des Schaums vorliegt.

22. Arzneimittelzubereitung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß sie eine Kombination aus einem nikotinergen Wirkstoff und einem Antidepressivum enthält.

23. Verwendung einer Darreichungsform nach einem oder mehreren der Ansprüche 1 bis 22 zur rektalen, vaginalen oder intranasalen Verabreichung von pharmazeutischen Wirkstoffen an Menschen oder Tiere.

24. Verwendung einer Wirkstoffkombination aus nikotinergem Wirkstoff und Psychopharmakon zur Herstellung einer oralen

Darreichungsform nach einem der vorhergehenden Ansprüche zur Raucherentwöhnung.

25. Verwendung einer Wirkstoffkombination aus nikotinergem Wirkstoff und Antidepressivum zur Herstellung einer oralen Darreichungsform nach einem der vorhergehenden Ansprüche zur Raucherentwöhnung.

26. Verwendung nach einem oder mehreren der Ansprüche 23 - 26, dadurch gekennzeichnet, daß das Arzneimittel als Wafer formuliert wird.

27. Verfahren zur therapeutischen Behandlung einer unter Entzugserscheinungen der Raucherentwöhnung leidenden Person, dadurch gekennzeichnet, daß die Verabreichung der Wirkstoffkombination aus nikotinergem Wirkstoff und Psychopharmakon mittels einer oral applizierbaren Darreichungsform mit transmukosaler Resorption erfolgt.

28. Verfahren zur Herstellung einer flächenförmigen Darreichungsform nach einem der Ansprüche 1 bis 22, gekennzeichnet durch das

- Herstellen einer Lösung, die zumindest ein Polymer und mindestens zwei Wirkstoffe enthält, von denen einer Nikotin, ein Nikotinsalz, ein Nikotinderivat oder eine nikotinerg wirkende Substanz und der andere ein Psychopharmakon ist;
- Ausstreichen der Lösung auf eine Beschichtungsunterlage und
- Verfestigen der ausgestrichenen Lösung durch Trocknen und Entzug des Lösemittels.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038696

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/5513(2006.01)i, A61K 31/355(2006.01)i, A61K 9/16(2006.01)i, A61K 47/10(2006.01)i, A61P 25/22(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS, Google scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007043057 A2 (TOUITOU, ELKA et. al.) 19 April 2007 See claims 18 and 35, p. 6 (line 1-3), 8 (line 3-11)	1-19
A	WO 2005117830 A1 (CAMURUS AB, SWED) 15 December 2005 See whole document	1-19
A	WO 2006075123 A1 (CAMURUS AB, SWED) 20 July 2006 See whole document	1-19
A	WO 2007144081 A2 (LTS LOHMANN THERAPIE-SYSTEM A.-G.) 21 December 2007 See whole document ----------//	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 SEPTEMBER 2009 (28.09.2009)	**28 SEPTEMBER 2009 (28.09.2009)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea	KIM, YONG
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8164

Form PCT/ISA/210 (second sheet) (July 2008)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/42311

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/62; A61K 31/55 (2012.01)
USPC - 514/220-221
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC-514/220-221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-424/400, 434 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST, Google Scholar, Google, Intranasal, nasal, inhalation, mucosal, drug, delivery, denzodazepine, diazepam, tocopherol, tocotrienol, Vitamin E, alcohol, ethanol, benzyl alcohol, alkyl glycoside

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0258865 A1 (Cartt et al.) 15 October 2009 (15.10.2009) para [0010]-[0021], [0024]-[0030], [0035]-[0039], [0047], [0138], [0142]-[0143], [0147], [0161]-[0162], [0180]-[0181], [0196]-[0204]	1-62
A	US 2009/0130216 A1 (Cartt et al.) 21 May 2009 (21.05.2009) entire document	1-62
A	US 2008/0279784 A1 (Cartt et al.) 13 November 2008 (13.11.2008) entire document	1-62
A	US 2009/0304801 A1 (Liversidge et al.) 10 December 2009 (10.12.2009) entire document	1-62

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2012 (10.08.2012)	31 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Electronic Acknowledgement Receipt

EFS ID:	14255341
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Lori Holslin
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	16-NOV-2012
Filing Date:	27-MAR-2009
Time Stamp:	18:29:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	35401-716-201_IDS_Transmittal_11-16-2012.pdf	84271 439c472740d4cadb9a814d441410eba37fe76dd7	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	35401-716-201_IDS_11-16-2012.pdf	39964 6d414c0363cab7292d0f46f36b4f5b040739dbbe	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO2005-117830.pdf	6218647 4150cebea90f7f7df4a044b5617b2760326d040f	no	69
Warnings:					
Information:					
4	Foreign Reference	WO2006-075123.pdf	5620634 315663aef55ccda966a7a402b7a93b6b5b03f3ef	no	62
Warnings:					
Information:					
5	Foreign Reference	WO2007-043057.pdf	4736531 058fb2520a116d3c5c07180232c60268022a8156	no	63
Warnings:					
Information:					
6	Foreign Reference	WO2007-144081.pdf	1836909 49827b9fb26659e7ae1302d3187142a5a28da65d	no	25
Warnings:					
Information:					
7	Non Patent Literature	PCT-US09-038696-ISR.pdf	34728 548174406b3b2c5b8d0943ac71626cc8f7d2565d	no	1
Warnings:					
Information:					
8	Non Patent Literature	PCT-US12-42311-ISR.pdf	38141 7a99b9ea862f5c3947435e677508e64fd0d4d109	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	18609825		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve CARTT, et al.	Group Art Unit: 1612
Serial Number: 12/413,439	Examiner: MILLIGAN, ADAM C.
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: November 16, 2012

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Sir:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☒ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the

requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: 11/16/2012

By: _____
Matthew V. Grumbling
Reg. No. 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam Milligan
Sheet	1	of	3	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2001-0042932	11/22/2001	Mathiowitz et al.	
	2.	US-2002-0127278	09/12/2012	Kipp	
	3.	US-2002-0168402	11/14/2002	Kipp	
	4.	US-2003-0031719	02/13/2003	Kipp	
	5.	US-2006-0198896	09/07/2006	Liversidge et al.	
	6.	US-2008-0200418	08/21/2008	Maggio	
	7.	US-2008-0248123	10/09/2008	Swanson et al.	
	8.	US-2008-0299079	12/04/2008	Meezan et al.	
	9.	US-2009-0163447	06/25/2009	Maggio	
	10.	US-2009-0297619	12/03/2009	Swanson et al.	
	11.	US-2010-0068209	03/18/2010	Maggio	
	12.	US-2011-0172211	07/14/2011	Back et al.	
	13.	US-2011-0257096	10/20/2011	Maggio	
	14.	US-2012-0196941	08/02/2012	Maggio	
	15.	US-2013-0065886	03/14/2013	Cartt	
	16.	US-4,973,465	11/27/1990	Baurain et al.	
	17.	US-5,457,100	10/10/1995	Daniel	
	18.	US-5,661,130	08/26/1997	Meezan et al.	
	19.	US-5,861,510	01/19/1999	Piscipio et al.	
	20.	US-5,863,949	01/26/1999	Robinson et al.	
	21.	US-6,143,211	11/07/2000	Mathiowitz et al.	
	22.	US-6,193,985	02/27/2001	Sonne	
	23.	US-6,235,224	05/22/2001	Mathiowitz et al.	
	24.	US-6,428,814	08/06/2002	Bosch et al.	
	25.	US-6,610,271	08/26/2003	Wermeling	
	26.	US-6,616,914	09/09/2003	Ward et al.	
	27.	US-6,627,211	09/30/2003	Choi et al.	

Examiner Signature		Date Considered	

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 3

Complete if Known	
Application Number	12/413,439
Filing Date	03/27/2009
First Named Inventor	Steve Cartt
Art Unit	1612
Examiner Name	Adam Milligan
Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-6,908,626	06/21/2005	Cooper et al.	
	29.	US-7,132,112	11/07/2006	Choi et al.	
	30.	US-7,434,579	10/14/2008	Young et al.	

U.S. PROVISIONAL PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Filing Date MM-DD-YYYY	Name of Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	31.	U.S. Prov. Appl. No. 60/148,464	08/12/1999	Noe	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	32.	EP-00780386	6/25/1997	Hoffman-La Roche AG		
	33.	EP-0818442	1/14/1998	Pfizer Inc.		
	34.	EP-0945485	9/29/1999	Morton Int'l., Inc.		
	35.	EP-1004578	5/31/2000	Pfizer Products Inc.		
	36.	EP-606046	7/13/1994	CIBA-GEIGY AG		
	37.	EP-931788	7/28/1999	Pfizer Limited		
	38.	JP 2003-505403 (w/ Corresponding English equivalent WO-0106987)	2/12/2003	SK Corpororation (US)		X
	39.	JP 2005-508939 (w/ Corresponding English equivalent WO-03030872)	4/7/2005	Cooper, Eugene R.		X
	40.	JP 2007-510722 (w/ Corresponding English equivalent WO-2005-044234)	4/26/2007	Elan Pharma International Ltd.		X
	41.	WO-1990-05719	5/31/1990	British Bio-		

Examiner Signature		Date Considered	

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.* [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam Milligan
Sheet	3	of	3	Attorney Docket Number	35401-716.201

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
				Technology Ltd.		
	42.	WO-1996-27583	9/12/1996	Pfizer Inc.		
	43.	WO-1996-33172	10/24/1996	Pfizer Inc.		
	44.	WO-1998-03516	1/29/1998	Pfizer Inc.		
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Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

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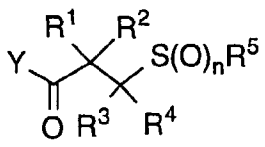
(54) Matrix metalloprotease inhibitors

(57) Compounds of the formula:



I

wherein:

n is 0, 1 or 2;

Y is hydroxy or XONH-, where X is hydrogen or lower alkyl;

R^1 is hydrogen or lower alkyl;

R^2 is hydrogen, lower alkyl, heteroalkyl, aryl, aralkyl, arylheteroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heteroarylheteroalkyl, heterocyclo, heterocylo-lower alkyl, heterocyclo-lower heteroalkyl or $-NR^6R^7$, wherein:

R^6 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl, aryl, heteroaryl and heteroaralkyl;

R^7 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)R^8$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-SO_2R^{10}$, aryloxycarbonyl, or alkoxycarbonyl; or R^6 and R^7 together with the nitrogen atom to which they are attached represent a heterocyclo group; wherein

R^8 and R^9 are independently hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heteroalkyl; and

R^{10} is lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroalkyl or heterocyclo; or

R^1 and R^2 together with the carbon atom to which they are attached represent a cycloalkyl or heterocyclo group;

R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl,

(Cont. next page)

heteroaralkyl, heteroalkyl or lower alkoxy;

R^4 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl; or

R^2 and R^3 together with the carbons to which they are attached represent a cycloalkyl or heterocyclo group; or

R^3 and R^4 together with the carbon to which they are attached represent a cycloalkyl or heterocyclo group; and

R^5 is lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

or pharmaceutically acceptable salts or esters thereof exhibit useful pharmacological properties, in particular for use as matrix metalloprotease inhibitors, particularly for interstitial collagenases.

Description

The present invention relates to compounds of formula I and their pharmaceutically acceptable salts and esters thereof, that inhibit matrix metalloproteases, particularly interstitial collagenases, and are therefore useful in the treatment of mammals having disease states alleviated by the inhibition of such matrix metalloproteases.

Matrix metalloproteases ("MMPs") are a family of proteases (enzymes) involved in the degradation and remodeling of connective tissues. Members of this family of endopeptidase enzymes are present in various cell types that reside in or are associated with connective tissue, such as fibroblasts, monocytes, macrophages, endothelial cells, and invasive or metastatic tumor cells. MMP expression is stimulated by growth factors and cytokines in the local tissue environment, where these enzymes act to specifically degrade protein components of the extracellular matrix, such as collagen, proteoglycans (protein core), fibronectin and laminin. These ubiquitous extracellular matrix components are present in the linings of joints, interstitial connective tissues, basement membranes, and cartilage. Excessive degradation of extracellular matrix by MMPs is implicated in the pathogenesis Of many diseases, including rheumatoid arthritis, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease, cerebral hemorrhaging associated with stroke, periodontal disease, aberrant angiogenesis, tumor invasion and metastasis, corneal ulceration, and in complications of diabetes. MMP inhibition is, therefore, recognized as a good target for therapeutic intervention.

The MMPs share a number of properties, including zinc and calcium dependence, secretion as zymogens, and 40-50% amino acid sequence homology. The MMP family currently consists of at least eleven enzymes, and includes collagenases, stromelysins, gelatinases, matrilysin, metalloelastase, and membrane-type MMP, as discussed in greater detail below.

Interstitial collagenases catalyze the initial and rate-limiting cleavage of native collagen types I, II, and III. Collagen, the major structural protein of mammals, is an essential component of the matrix of many tissues, for example, cartilage, bone, tendon and skin. Interstitial collagenases are very specific matrix metalloproteases which cleave these collagens to give two fragments which spontaneously denature at physiological temperatures and therefore become susceptible to cleavage by less specific enzymes. Cleavage by the collagenases results in the loss of structural integrity of the target tissue, essentially an irreversible process. There are currently three known human collagenases. The first is human fibroblast-type collagenase (HFC, MMP-1, or collagenase-1) that is produced by a wide variety of cells including fibroblasts and macrophages. The second is human neutrophil-type collagenase (HNC, MMP-8, or collagenase-2) that has so far only been demonstrated to be produced by neutrophils. The most recently discovered member of this group of MMPs is human collagenase-3 (MMP-13) which was originally found in breast carcinomas, but has since shown to be produced by chondrocytes. The only collagenase known to exist in rodents is the homolog of human collagenase-3.

The gelatinases include two distinct, but highly related, enzymes: a 72-kD enzyme (gelatinase A, HFG, MMP-2) secreted by fibroblasts and a wide variety of other cell types, and a 92-kD enzyme (gelatinase B, HNG, MMP-9) released by mononuclear phagocytes, neutrophils, corneal epithelial cells, tumor cells, cytotrophoblasts and keratinocytes. These gelatinases have been shown to degrade gelatins (denatured collagens), collagen types IV (basement membrane) and V, fibronectin and insoluble elastin.

Stromelysins 1 and 2 have been shown to cleave a broad range of matrix substrates, including laminin, fibronectin, proteoglycans, and collagen types IV and IX in their non-helical domains.

Matrilysin (MMP-7, PUMP-1) has been shown to degrade a wide range of matrix substrates including proteoglycans, gelatins, fibronectin, elastin, and laminin. Its expression has been documented in mononuclear phagocytes, rat uterine explants and sporadically in tumors. Other less characterized MMPs include macrophage metalloelastase (MME, MMP-12), membrane type MMP (MMP-14), and stromelysin-3 (MMP-11).

Inhibitors of MMPs provide useful treatments for diseases associated with the excessive degradation of extracellular matrix, such as arthritic diseases (rheumatoid arthritis and osteoarthritis), multiple sclerosis, bone resorptive diseases (such as osteoporosis), the enhanced collagen destruction associated with diabetes, chronic obstructive pulmonary disease, cerebral hemorrhaging associated with stroke, periodontal disease, corneal or gastric ulceration, ulceration of the skin, tumor invasion and metastasis, and aberrant angiogenesis. The involvement of individual collagenases in the degradation of tissue collagens probably depends markedly on the tissue. The tissue distribution of human collagenases suggests that collagenase-3 is the major participant in the degradation of the collagen matrix of cartilage, while collagenase-1 is more likely to be involved in tissue remodeling of skin and other soft tissues. Thus, inhibitors selective for collagenase-3 over collagenase-1 are preferred for treatment of diseases associated with cartilage erosion, such as arthritis, etc.

Inhibitors of MMP also are known to substantially inhibit the release of tumor necrosis factor (TNF) from cells, and which therefore may be used in the treatment of conditions mediated by TNF. Such uses include, but are not limited to, the treatment of inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, restinosis, aneurysmal disease, graft versus host reactions and autoimmune disease.

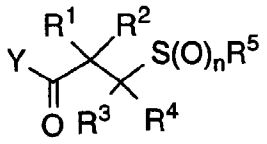
In addition to these effects on the release of TNF from cells, MMP inhibitors have also been shown to inhibit the

release of other biologically active molecules from cells, including soluble receptors (CD30 and receptors for TNF (p55 and p75), IL-6, IL-1 and TSH), adhesion molecules (*e.g.,* L-selection, ICAM-1, fibronectin) and other growth factors and cytokines, including Fas ligand, TGF-a, EGF, HB-EGF, SCF and M-CSF. Inhibition of the release or shedding of such proteins may be of benefit in a number of disease states, including rheumatoid arthritis, multiple sclerosis, vascular disease, Type II diabetes, HIV, cachexia, psoriasis, allergy, hepatitis, inflammatory bowel disease, and cancer.

Since non-specific inhibition of the shedding enzymes (sheddases) may have opposite pharmacological effects, selectivity will be a particular advantage, *e.g.,* the inhibition of TNF release without the concurrent inhibition of TNF receptor release.

The design and uses of MMP inhibitors is described, for example, in *J. Enzyme Inhibition,* **2**, 1-22 (1987); *Drug News & Prospectives,* **3**(8), 453-458 (1990); *Arthritis and Rheumatism,* **36**(2), 181-189 (1993); *Arthritis and Rheumatism,* **34**(9), 1073-1075 (1991); *Seminars in Arthritis and Rheumatism,* **19**(4), Supplement 1 (February), 16-20 (1990); *Drugs of the Future,* **15**(5), 495-508 (1990); and *J. Enzyme Inhibition,* **2**, 1-22 (1987). MMP inhibitors are also the subject of various patents and patent applications, for example, U.S. Patent Nos. 5,189,178 and 5,183,900, European Published Patent Applications 438 223, 606 426, and 276 436, and published Patent Cooperation Treaty International Applications WO 92/21360, WO 92/06966, WO 92/09563, and WO 94/25434.

One aspect of the invention concerns compounds represented by Formula I:



I

wherein:

n is 0, 1 or 2;

Y is hydroxy or XONH-, where X is hydrogen or lower alkyl;

R^1 is hydrogen or lower alkyl;

R^2 is hydrogen, lower alkyl, heteroalkyl, aryl, aralkyl, arylheteroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heteroarylheteroalkyl, heterocyclo, heterocylo-lower alkyl, heterocyclo-lower heteroalkyl or $-NR^6R^7$, wherein:

R^6 is hydrogen, lower alkyl, cycloalkyl or cycloalkyl alkyl, aryl, heteroaryl and heteroaralkyl;

R^7 is hydrogen, lower alkyl, cycloalkyl or cycloalkyl alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)R^8$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-SO_2R^{10}$, aryloxycarbonyl, or alkoxycarbonyl; or

R^6 and R^7 together with the nitrogen atom to which they are attached represent a heterocyclo group; wherein

R^8 and R^9 are independently hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heteroalkyl; and

R^{10} is lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroalkyl or heterocyclo; or

R^1 and R^2 together with the carbon atom to which they are attached represent a cycloalkyl or heterocyclo group;

R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroalkyl or lower alkoxy;

R^4 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl; or

R^2 and R^3 together with the carbons to which they are attached represent a cycloalkyl or heterocyclo group; or

R^3 and R^4 together with the carbon to which they are attached represent a cycloalkyl or heterocyclo group; and

R^5 is lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl; or heteroaralkyl;

or a pharmaceutically acceptable salt or ester thereof.

A second aspect of this invention relates to pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof admixed with at least one pharmaceutically acceptable excipient.

A third aspect of this invention relates to methods for treating mammals having a disease state alleviated by the inhibition of matrix metalloproteases, by administering an effective amount of a compound of Formula I, or a pharmaceutical composition thereof, to the mammal. Such disease states include arthritic diseases, multiple sclerosis, bone

resorption disease (such as osteoporosis), the enhanced collagen destruction associated with diabetes, chronic obstructive pulmonary disease, cerebral hemorrhaging associated with stroke, periodontal disease, corneal or gastric ulceration, ulceration of the skin, and tumor metastasis.

A fourth aspect of this invention relates to methods for preparing compounds of Formula I.

Among the family of compounds of the present invention as defined above, a particular family of compounds of formula I consists of n is 0, 1 or 2; Y is hydroxy or XONH-, where X is hydrogen or lower alkyl; R^1 is hydrogen or lower alkyl; R^2 is hydrogen, lower alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, or $-NR^6R^7$; or R^1 and R^2 together with the carbon atom to which they are attached represent a cycloalkyl or heterocyclo group; in which R^6 is hydrogen, lower alkyl, or phenyl; and R^7 is hydrogen, lower alkyl, benzyl, $-C(O)R^8$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-SO_2R^{10}$, benzyloxycarbonyl, or alkoxycarbonyl; or R^6 and R^7 together with the nitrogen atom to which they are attached represent a heterocyclo group; wherein R^8 and R^9 are independently hydrogen or lower alkyl; and R^{10} is lower alkyl, aryl, heteroaryl, or heterocyclo; R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, or lower alkoxy; R^4 is hydrogen or lower alkyl; or R^2 and R^3 together with the carbons to which they are attached represent a cycloalkyl or heterocyclo group; or R^3 and R^4 together with the carbon to which they are attached represent a cycloalkyl or heterocyclo group; and R^5 is lower alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl.

Within these families a preferred category includes compounds where n is 2 and Y is -NHOH.

Within this category, one preferred group includes the compounds where R^1 is hydrogen and R^5 is aryl. One preferred subgroup within this group includes the compounds where R^2 is hydrogen and R^3 is aralkyl, especially benzyl, and R^4 is hydrogen and R^5 is optionally substituted phenyl or naphthyl, more especially where R^5 is 4-methoxyphenyl, phenylthiophenyl, phenoxyphenyl, or biphenyl.

Another preferred subgroup within this group includes the compounds where R^3 and R^4 together with the carbon to which they are attached form a cycloalkyl group, especially cyclopentyl and cyclcohexyl, more especially in combination where R^5 is 4-methoxyphenyl or 4-phenoxyphenyl.

Yet another preferred subgroup within this group includes the compounds where R^3 and R^4 together with the carbon to which they are attached form a heterocyclo group, in particular optionally substituted piperidinyl or tetrahydropyranyl, especially piperidin-4-yl, 1-methylpiperidin-4-yl, 1-(cyclopropylmethyl)piperidin-4-yl, or tetrahydropyranyl, more especially in combination where R^5 is 4-phenoxyphenyl, 4-(4-chlorophenoxy)phenyl, 4-bromophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

Another preferred group within this category includes the compounds where R^2 is $-NR^6R^7$, R^1, R^3 and R^4 are hydrogen, and R^5 is aryl. One preferred subgroup within this group includes the compounds where R^5 is 4-phenoxyphenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl, especially where R^6 is hydrogen and R^7 is CBZ-valinamido, valinamido or dimethylaminosulfonyl.

Another preferred group within this category includes the compounds where R^1 and R^2 together with the carbon to which they are attached form a heterocyclo group. A preferred subgroup within the group includes compounds where R^3 and R^4 are hydrogen and R^1 and R^2 together with the carbon to which they are attached form a heterocyclo group, in particular optionally substituted piperidinyl or tetrahydropyranyl, especially piperidin-4-yl, 1-methylpiperidin-4-yl, 1-(cyclopropylmethyl)piperidin-4-yl, or most preferably tetrahydropyranyl, more especially in combination where R^5 is 4-phenoxyphenyl, 4-(4-chlorophenoxy)phenyl, 4-(4-bromophenoxy)phenyl, 4-(4-fluorophenoxy)phenyl, 4-(thiophen-2-yl)phenoxy)phenyl, 4-(thiophen-3-yl)phenoxy)phenyl, 4-(thiazol-2-yl)phenoxy)phenyl, 4-(2-pyridyloxy)phenyl, or 4-(5-chloro-2-pyridyloxy)phenyl.

Another preferred group within this category includes compounds wherein R^1 and R^2 are both alkyl, R^3 and R^4 are hydrogen. One preferred subgroup includes compounds wherein R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

Another group within this category includes compounds wherein R^2 and R^3 together with the carbons to which they are attached form a cycloalkyl group and R^5 is aryl. Preferably, the cycloalkyl group is cyclopentyl or cyclohexyl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

Preferred compounds are:

N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydropyran-4-yl]-acetamide;
2-{4-[4-(4-chlorophenoxy)-phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide;
2-{4-[4-(4-chlorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide;
N-hydroxy-2-[1-methyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide;
N-hydroxy-2-{1-methyl-4-[4-(4-chlorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-acetamide;
N-hydroxy-2-{1-methyl-4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-acetamide;
2-[1-cyclopropylmethyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-*N*-hydroxyacetamide;
2-{1-cyclopropylmethyl-4-[4-(4-chlorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide;

2-{1-cyclopropylmethyl-4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide;
N-hydroxy-2-[4-(4-phenoxyphenylsulfinyl)-tetrahydropyran-4-yl]-acetamide;
2-{4-[4-(4-chlorophenoxy)-phenylsulfinyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)-phenylsulfinyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
N-hydroxy-2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetamide;
2-{4-[4-(4-chlorophenoxy)-phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)-phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-bromophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-fluorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
3-[4-(4-chlorophenoxy)phenylsulfonyl]-2,2-dimethyl-*N*-hydroxypropionamide;
4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-(cyclopropylmethyl)piperidine-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-(nicotinoyl)piperidine-4-(*N*-hydroxycarboxamide);
4-[4-(phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(thiophen-2-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(thiophen-3-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(furan-2-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(benzofuran-2-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(thiazol-2-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(thiazol-4-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(thiazol-5-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(imidazol-1-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-(imidazol-2-yl)-phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(5-chloro-2-pyridyloxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide);
3-[4-(5-chloro-2-pyridyloxy)phenylsulfonyl]-2,2-dimethyl-*N*-hydroxypropionamide;
(R)-2-(CBZ-valinamido)-N-hydroxy-3-(4-phenoxyphenylsulfonyl)propionamide;
(R)-N-hydroxy-2-valinamido-3-(4-phenoxyphenylsulfonyl)-propionamide;
(R)-2-dimethylamino-N-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide;
(R)-2-dimethylaminosulfonamido-N-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide

and pharmaceutically acceptable salts thereof.

Definitions

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

"Alkyl" means a branched or unbranched saturated hydrocarbon chain containing 1 to 8 carbon atoms, such as methyl, ethyl, propyl, *tert*-butyl, *n*-hexyl, *n*-octyl and the like.

"Lower alkyl" means a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, *tert*-butyl, *n*-butyl, *n*-hexyl and the like, unless otherwise indicated.

The term "heteroalkyl" refers to a branched or unbranched, cyclic or acyclic saturated organic radical containing carbon, hydrogen and one or more heteroatom containing substituents independently selected from OR^a, NR^aR^b, and $S(O)_nR^a$ (where n is 0, 1 or 2) and R^a is hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or acyl, R^b is hydrogen, alkyl, cycloalkyl, aryl, aralkyl, acyl, alkylsulfonyl, carboxamido, or mono- or di-alkylcarbamoyl. Representative examples include hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxymethyl, N-acylaminoalkyl, thienylthiomethyl and the like.

"Acyl" refers to the group -C(O)-R', where R' is lower alkyl.

"Alkylene" refers to a straight chain or branched chain divalent radical consisting solely of carbon and hydrogen, containing no unsaturation and having from one to six carbon atoms, *e. g.,* methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, hexylene, and the like.

"Lower alkoxy" means the group -O-R', where R' is lower alkyl.

"Alkoxycarbonyl" means the group RO-C(O)- where R is alkyl as herein defined.

"Alkoxycarbonylalkyl" means the group $ROC(O)(CH_2)_n$- where R is alkyl as herein defined and n is 1, 2 or 3.

"Aryl" refers to a monovalent aromatic carbocyclic radical having a single ring (*e.g.,* phenyl) or two condensed rings (*e.g.,* naphthyl), which can optionally be mono-, di- or tri-substituted, independently, with hydroxy, carboxy, lower alkyl, cycloalkyl, cycloalkyloxy, lower alkoxy, chloro, fluoro, trifluoromethyl and/or cyano. The ring(s) can alternatively be optionally monosubstituted with the group R^a-Z-, where Z is oxygen, sulfur, -CH=CH-, $-CH_2$, carbonyl, a covalent bond, or nitrogen optionally substituted with lower alkyl, and R^a is a monovalent aromatic carbocyclic, heteroaryl or heterocyclo radical, or a combination thereof, having 1 or 2 rings, for example phenyl, pyridyl, thienyl, imidazolyl, furanyl, pyrimidinyl, benzothiophene, azanaphthalene, indolyl, phenyl-(furan-2-yl), phenyl-(thien-2-yl), phenyl-(thien-3-yl), phenyl-

(imidazol-2-yl), phenyl-(thiazol-2-yl), phenyl-(morpholin-2-yl), and phenyl-(oxazol-2-yl), (the ring(s) represented by R^a being optionally mono-or disubstituted by hydroxy, carboxy, lower alkyl, lower alkoxy, halo, trifluoromethyl and/or cyano). Examples of aryl substituted by R^a-Z- are benzoyl, diphenylmethane, biphenyl, 6-methoxybiphenyl, 4-(4-methylphenoxy)phenyl, 4-phenoxyphenyl, 2-thiophenoxyphenyl, 4-pyridethenylphenyl, 4-(thiophen-2-yl)phenoxyphenyl, 4-(thiophen-3-yl)phenoxyphenyl, 4-(2-pyridyloxy)phenyl, 4-(5-chloro-2-pyridyloxy)phenyl, 4-(thiazol-5-yl)phenoxyphenyl, 4-(imidazol-2-yl)phenoxyphenyl, and the like.

"Heteroaryl" refers to a monovalent aromatic carbocyclic radical having one or two rings incorporating one, two or three heteroatoms (chosen from N, O or S) within the ring(s), such as thiazole, oxazole, imidazole, thiophene, quinolyl, benzofuranyl, pyridyl, and indolyl, which can optionally be mono-, di- or tri-substituted, independently, with OH, COOH, lower alkyl, lower alkoxy, halo, trifluoromethyl and/or cyano.

"Aralkyl" refers to a radical of the formula R^b-R^c-, wherein R^b is aryl as defined above and R^c is alkylene as defined above, for example benzyl, phenylethylene, 3-phenylpropyl, biphenylpropyl.

"Benzyloxycarbonyl" refers to a radical of the formula $R^dCH_2OC(O)$-, where R^d is phenyl. "Benzyloxycarbonylamino" refers to a radical of the formula $R^dCH_2OC(O)NH$-, where R^d is phenyl.

"Cycloalkyl" means a saturated monovalent monocyclic hydrocarbon radical containing 3-8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

"Cycloalkylalkyl" means cycloalkyl as defined above attached to an alkylene radical as defined above.

"Halo" refers to bromo, chloro or fluoro.

"Heteroaralkyl" refers to a radical of the formula R^eR^c-, where R^e is heteroaryl as defined above and R^c is alkylene as defined above.

"Heterocyclo" refers to a monovalent saturated carbocyclic radical, consisting of either a 5 to 7 membered monocyclic ring or a 9 to 14 membered bicyclic ring, substituted by one, two or three heteroatoms chosen from N, O, or S, optionally fused to a substituted or unsubstituted benzene ring. Examples of heterocyclo radicals are morpholino, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl-1,1-dioxide, tetrahydropyranyl, and the like, which can be optionally substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylamino, alkylaminoalkyl, acyl valyl, alkylsulfonyl, dialkylamino, heteroaroyl, alkoxycarbonylalkyl, and an amino protecting group where appropriate (*e.g.* CBZ, for example, 1-CBZ-piperidin-4-yl). However, the definition "R^6 and R^7 together with the nitrogen to which they are attached represent a heterocyclo group" clearly can refer only to a heterocyclo group containing at least one nitrogen atom.

"Hydroxylamino" refers to the group -NHOH.

"BOC" refers to *tert*-butoxycarbonyl.

"CBZ" refers to benzyloxycarbonyl.

"DCC" refers to 1,3-dicyclohexylcarbodiimide.

"Valine amide" refers to the radical $(CH_3)_2CHCH(NH_2)C(O)NH$-.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted phenyl or aryl" means that the phenyl or aryl moiety may or may not be substituted and that the description includes both substituted and unsubstituted phenyl. The phrase "optional pharmaceutical excipients" indicates that a composition or dosage form so described may or may not include pharmaceutical excipients other than those specifically stated to be present, and that the formulation or dosage form so described includes instances in which optional excipients are present and instances in which they are not.

"Amino-protecting group" as used herein refers to those organic groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures, and includes, but is not limited to, benzyl, acyl, benzyloxycarbonyl (carbobenzyloxy), *p*-methoxybenzyloxy-carbonyl, *p*-nitrobenzyloxycarbonyl, *tert*-butoxycarbonyl, trifluoroacetyl, and the like.

"Base" as used here includes both strong inorganic bases such as sodium hydroxide, lithium hydroxide, ammonium hydroxide, potassium carbonate and the like, and organic bases such as pyridine, diisopropylethylamine, 4-methylmorpholine, triethylamine, dimethylaminopyridine and the like.

"Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids and which are not biologically or otherwise undesirable. If the compound exists as a free base, the desired acid salt may be prepared by methods known to those of ordinary skill in the art, such as treatment of the compound with an inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or with an organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. If the compound exists as a free acid, the desired base salt may also be prepared by methods known to those of ordinary skill in the art, such as the treatment of the compound with an inorganic base or an organic base. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of

primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like.

"Pharmaceutically acceptable ester" as used herein refers for example to those non-toxic esters of a compound of Formula I where R^1 is hydroxy, and are formed by reaction of such compounds, by means well known in the art, with an appropriate alkanol of 1-8 carbon atoms, for example methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, *tert*-butanol, *i*-butanol (or 2-methylpropanol), *n*-pentanol, *n*-hexanol, and the like.

The terms "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith, including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), *N,N*-dimethylformamide ("DMF"), chloroform ("$CHCl_3$"), methylene chloride (or dichloromethane or "CH_2Cl_2"), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *tert*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as mixtures of stereoisomers or as individual (*R*)- or (*S*)- stereoisomers. The individual enantiomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis. It is understood that the individual (*R*)- or (*S*)-stereoisomers as well as racemic mixtures and other mixtures of stereoisomers are encompassed within the scope of the present invention.

The use of the symbol "(*R*)" or "(*S*)" preceding a substituent designates the absolute stereochemistry of that substituent according to the Cahn-Ingold-Prelog rules [see Cahn et al., *Angew. Chem. Inter. Edit.,* **5**, 385 (1966), ertata p. 511; Cahn et al., *Angew. Chem.,* **78**, 413 (1966); Cahn and Ingold, *J. Chem. Soc.,* (London), 612 (1951); Cahn et al., *Experientia,* **12**, 81 (1956); Cahn J., Chem. Educ., **41**, 116 (1964)]. Because of the interrelation of the designated substituent with the other substituents in a compound having a or β prefixes, the designation of the absolute configuration of one substituent fixes the absolute configuration of all substituents in the compound and thus the absolute configuration of the compound as a whole.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. Enantiomers rotate the plane of polarized light in opposite directions. The enantiomer that rotates the plane to the left is called the levo isomer, and is designated (-). The enantiomer that rotates the plane to the right is called the dextro isomer, and is designated (+).

"Diastereoisomers" are stereoisomers which are not mirror-images of each other.

"Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers.

"Mammal" includes humans and all domestic and wild animals, including, without limitation, cattle, horses, swine, sheep, goats, dogs, cats, and the like.

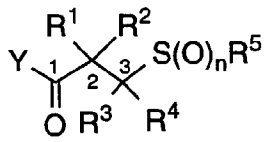
"Treating" or "treatment" as used herein cover the treatment of a disease-state in a mammal, particularly in a human, and include:

(i) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it;
(ii) inhibiting the disease-state, *i.e.,* arresting its development; or
(iii) relieving the disease-state, *i.e.,* causing regression of the disease-state.

The term "therapeutically effective amount" refers to that amount of a compound of Formula I that is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

Nomenclature

The compounds of Formula I, illustrated below, will be named using the indicated numbering system:



A compound of Formula I wherein is Y is *N*-hydroxylamino; R^1 and R^2 are hydrogen; R^3 is benzyl; R^4 is hydrogen; R^5 is 4-methoxyphenyl; and n is 2, is named 3-benzyl-3-(4-methoxyphenylsulfonyl)-*N*-hydroxypropionamide.

A compound of Formula I wherein Y is *N*-hydroxylamino; R^1 and R^2 are hydrogen; R^3 and R^4 together with the carbon to which they are attached represent tetrahydropyran-4-yl; R^5 is 4-(4-fluorophenoxy)phenyl; and n is 2, is named as an acetic acid derivative, *i.e.,* 2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxy-acetamide.

A compound of Formula I wherein Y is hydroxy; R^1 is hydrogen; R^2 is methyl; R^3 and R^4 together with the carbon to which they are attached represent 1-methylpiperidin-4-yl; R^5 is biphenyl; and n is 1, is named 2-[4-(biphenyl-4-sulfinyl)-1-methylpiperidin-4-yl]-propionic acid.

A compound of Formula I wherein Y is *N*-hydroxylamino; R^1 and R^2 together with the carbon to which they are attached represent tetrahydropyran-4-yl, R^3 and R^4 are hydrogen, R^5 is 4-(4-chlorophenoxy)-phenyl; and n is 2, is named 4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide).

Synthetic Reaction Parameters

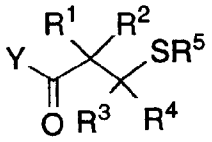
Unless specified to the contrary, the reactions described herein take place at atmospheric pressure within a temperature range from 5°C to 100°C (preferably from 10°C to 50°C; most preferably at "room" or "ambient" temperature, *e.g.,* 20°C). Further, unless otherwise specified, the reaction times and conditions are intended to be approximate, *e.g.,* taking place at about atmospheric pressure within a temperature range of about 5°C to about 100°C (preferably from about 10°C to about 50°C; most preferably about 20°C) over a period of about 1 to about 10 hours (preferably about 5 hours). Parameters given in the Examples are intended to be specific, not approximate.

Amide couplings used to form the compounds of Formula I are generally performed by the carbodiimide method with reagents such as 1,3-dicyclohexylcarbodiimide or *N'*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide hydrochloride or alternatively 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), in the presence of 1-hydroxybenzotriazole hydrate (HOBT) in an inert solvent such as *N,N*-dimethylformamide (DMF) or methylene chloride (CH_2Cl_2). Other methods of forming the amide or peptide bond include, but are not limited to, synthetic routes via an acid chloride, acyl azide, mixed anhydride or activated ester such as a *p*-nitrophenyl ester. Typically, solution phase amide couplings with or without peptide fragments are performed.

The selection of amino protecting groups used in the preparation of compounds of Formula I is dictated in part by the particular amide coupling conditions, and in part by the components involved in the coupling. Amino-protecting groups commonly used include those which are well-known in the art, for example, benzyloxycarbonyl (carbobenzyloxy) (CBZ), *p*-methoxybenzyloxycarbonyl, *p*-nitro-benzyloxycarbonyl, *N-tert*-butoxycarbonyl (BOC), and the like. It is preferred to use either BOC or CBZ as the protecting group for the a-amino group because of the relative ease of removal by mild acids in the case of BOC, *e.g.,* by trifluoroacetic acid (TFA) or hydrochloric acid in ethyl acetate; or removal by catalytic hydrogenation in the case of

PREPARATION OF COMPOUNDS OF FORMULA I

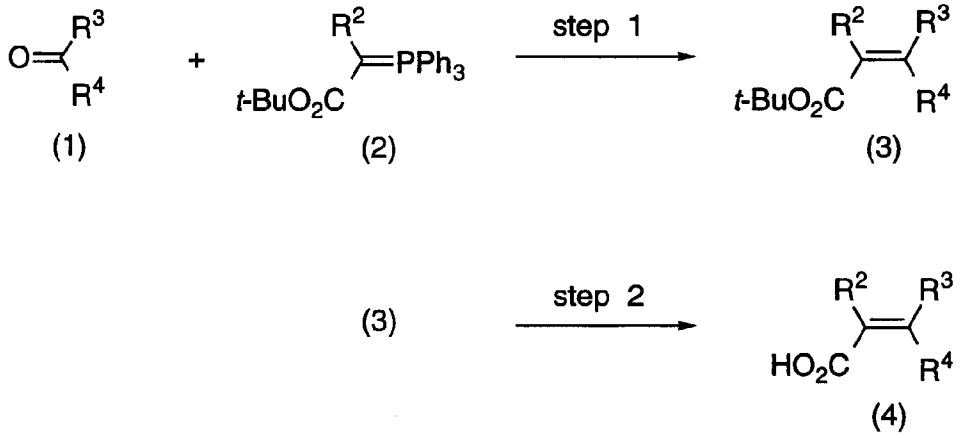
One method for preparing a compound of the Formula I, in particular wherein n is 1 or 2; Y is hydroxy or XONH-, where X is hydrogen or lower alkyl; R^1 is hydrogen or lower alkyl; R^2 is hydrogen, lower alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, or heterocyclo; or R^1 and R^2 together with the carbon atom to which they are attached represent a cycloalkyl or heterocyclo group; R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, or lower alkoxy; R^4 is hydrogen or lower alkyl; or R^2 and R^3 together with the carbons to which they are attached represent a cycloalkyl or heterocyclo group; or R^3 and R^4 together with the carbon to which they are attached represent a cycloalkyl or heterocyclo group; and R^5 is lower alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; comprises contacting a compound of the Formula:



with an oxidizing agent. Suitable oxidation conditions are outlined in the description of reaction scheme VIII below.

One method of preparing compounds of Formula I where n is 0, R^1 is hydrogen and R^2 is not $-NR^6R^7$ is from the corresponding unsaturated acid of Formula (4), the preparation of which is shown below in Reaction Scheme I:

REACTION SCHEME I



Starting Materials

Aldehydes and ketones of Formula (1) are commercially available, for example from Aldrich Chemical Co., or may be prepared as shown below, or prepared according to methods well known to those skilled in the art. The ylides of Formula (2) are commercially available, for example, (*tert*-butoxycarbonylmethylene)triphenylphosphorane is available from Aldrich, or may be prepared by standard methods known to those skilled in the art, for example by reacting the appropriate bromo derivative of formula $R^2CHBrCO_2$-(*tert*-butyl) with triphenylphosphine, and reacting the resulting triphenylphosphonium bromide derivative with a strong base.

Step 1 - Preparation of Compounds of Formula (3)

In general, a solution of an aldehyde or ketone compound of Formula (1) is reacted in an inert organic solvent, for example benzene, with a compound of Formula (2) (or alternatively, the corresponding phosphonate, for example trimethyl phosphonoacetate) for a period of 8 to 48 hours at 15°C to 30°C (aldehydes), preferably 20°C, or 70°C to 90°C (ketones), preferably 80°C, until starting material is consumed. The reaction product, an enoic ester of Formula (3), is isolated and purified by conventional means.

Step 2 - Preparation of Compounds of Formula (4)

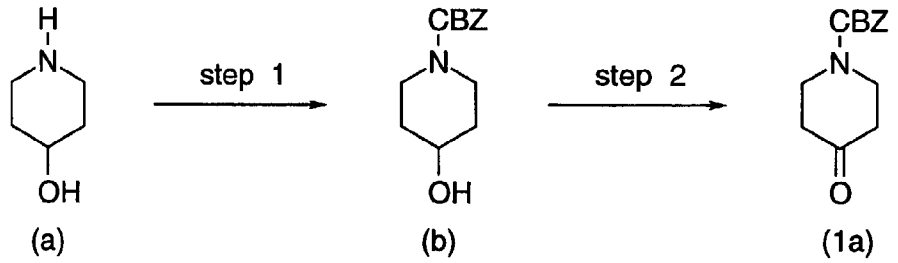
The compound of Formula (3) is then hydrolyzed under acidic conditions, optionally in the presence of an inert solvent, *e.g.,* treatment with trifluoroacetic acid in methylene chloride for about 20 minutes to 3 hours. The reaction is carried out at a temperature range from about 0°C to 40°C, preferably at about room temperature. In the case where trimethyl phosphonoacetate is used in Step 1, a methyl ester is produced which may be hydrolyzed conventionally

under basic conditions, for example sodium hydroxide in aqueous methanol or ethanol. The reaction product, an enoic acid of Formula (4), is isolated and purified by conventional means.

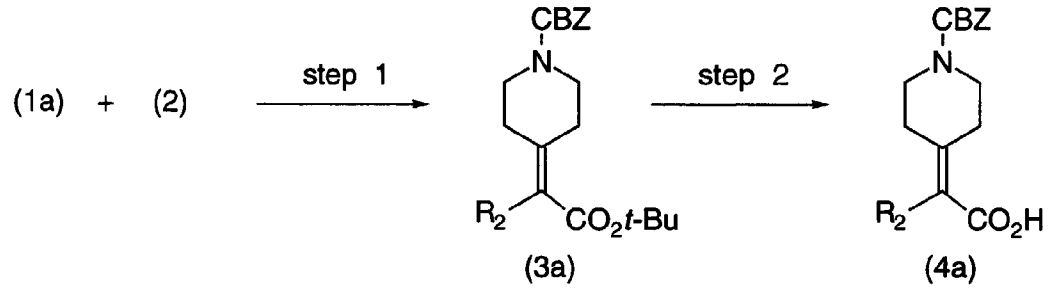
Preparation of Compounds of Formula (4) where R^3 and R^4 together with the Carbon to which they are attached represent a Piperidine Derivative

The preparation of compounds of Formula (4) where R^3 and R^4 together with the carbon to which they are attached represent a piperidine derivative, represented below as a compound of Formula (4a), in general requires the protection of the NH group. An example is shown below in Reaction Scheme II.

REACTION SCHEME II



(a) (b) (1a)



(3a) (4a)

Step 1 - Preparation of Compounds of Formula (b)

In general, a solution of a hydroxypiperidine compound of Formula (a) is protected by reaction of (a) in an inert organic solvent, for example tetrahydrofuran, in the presence of an excess of a tertiary base, for example triethylamine, with an equimolar amount of benzyl chloroformate. The reaction is carried out in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 10 to 30 hours, preferably about 18 hours. The reaction product of Formula (b) is isolated and purified by conventional means.

Step 2 - Preparation of Compounds of Formula (1a)

A compound of Formula (1a) is a compound of Formula (1) where R^3 and R^4 together with the carbon to which they are attached represent a protected piperidine derivative.

In general, a solution of a compound of Formula (b) is oxidized to a ketone of Formula (1a) by reaction of (b) in an inert organic solvent, for example methylene chloride, with an oxidizing agent, for example pyridinium chlorochromate, preferably in the presence of an inert support, for example Celite. The reaction is carried out in the temperature range

from about 0°C to 40°C, preferably at about 25°C, for about 10 to 30 hours, preferably about 18 hours. The reaction product of Formula (1a) is isolated and purified by conventional means.

Alternatively, reaction of commercially available 4-piperidone monohydrate hydrochloride with benzyl chloroformate under Schotten-Baumann conditions gives a compound of Formula (1a) in a single step.

Preparation of Compounds of Formula (4) where R^3 and R^4 Together with the Carbon to which they are attached Represent a Piperidine Derivative

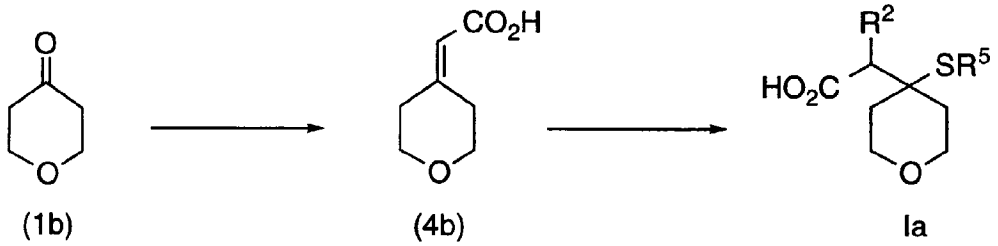
A compound of Formula (4) where R^3 and R^4 together with the carbon to which they are attached represent a piperidine derivative is represented as a compound of Formula (4a).

The protected piperidine ketone of Formula (1a) is converted to (3a), which is hydrolyzed to (4a) as described in Reaction Scheme I, Steps 1 and 2. The compound of Formula (4a) is then converted to a compound of Formula I where n is 0 as described in Reaction Scheme III below. The benzyloxycarbonyl (CBZ) protecting group is removed by catalytic hydrogenation, to give a compound of Formula I where R^3 and R^4 together with the carbon to which they are attached represent piperidine.

Preparation of Compounds of Formula (4) where R^3 and R^4 Together with the Carbon to which they are attached Represent a Pyran Derivative

Compounds of Formula (4) where R^3 and R^4 together with the carbon to which they are attached represent a tetrahydropyran derivative, represented as Formula (4b), are prepared similarly to the procedure shown above, starting from the corresponding 4-oxotetrahydropyran. The reaction is shown below in Reaction Scheme III and described in Example 3.

REACTION SCHEME III



The tetrahydropyran derivative of Formula (4b) is then converted to the corresponding compound of Formula I, *i.e.*, a compound of Formula I where n is 0, as described in Reaction Scheme VII.

Preparation of Compounds of Formula (4) where R^3 and R^4 Together with the Carbon to which they are Attached represent a Tetrahydrothiopyran-1,1-dioxide Derivative

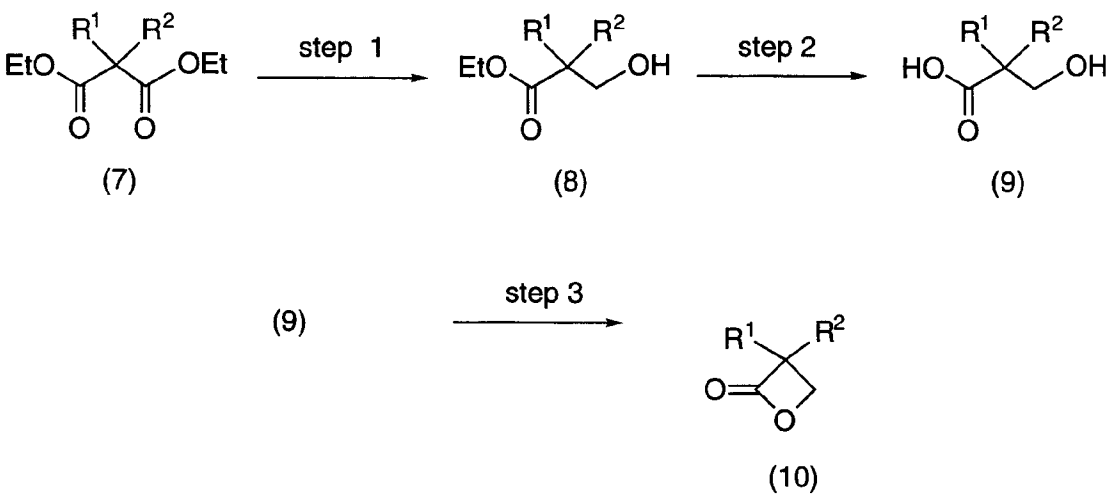
Compounds of Formula (4) where R^3 and R^4 together with the carbon to which they are attached represent a tetrahydrothiopyran1,1-dioxide derivative are prepared similarly to the procedure shown above, starting from the corresponding 4-oxotetrahydrothiopyran.

The tetrahydrothiopyran-1,1-dioxide derivative of Formula (4) is then converted to the corresponding compound of Formula I where n is 0 as described in Reaction Scheme III.

Alternative Preparation of Compounds of Formula I

Another method of preparing compounds of Formula I where R^2 is not $-NR^6R^7$ and R^3 and R^4 are both hydrogen is from the corresponding lactone of Formula (10), the preparation of which is shown below in Reaction Scheme IV.

REACTION SCHEME IV



Step 1 - Preparation of Compounds of Formula (8)

The starting compounds of Formula (7) are commercially available, or may be prepared by means well known in the art starting from diethyl malonate, *e.g.*, Gibson and Johnson, *J. Chem. Soc.*, p2525 (1930), (other diesters may be employed in place of the diethyl ester if desired). In general, a solution of a compound of Formula (7) is dissolved in an inert aromatic solvent, preferably benzene or toluene, and cooled to about -40° to -20°C, preferably about -30°C. To this cold solution is added a suitable hindered reducing agent, preferably diisobutylaluminum hydride in an inert aromatic solvent, maintaining the temperature at no higher than about 25°C. After the addition is complete, the reaction is maintained at about 15°C until all the starting material is consumed. After about 10 minutes the reaction is quenched by addition of a protic solvent, preferably ethanol, maintaining the temperature at no higher than about -15°C. Sodium borohydride is optionally added, but preferably the reaction is simply allowed to warm to about room temperature. The reaction product of Formula (8) is isolated and purified by conventional means.

Step 2 - Preparation of Compounds of Formula (9)

In general, the compound of Formula (8) is hydrolysed with a base to form the hydroxymethyl acid of Formula (9).

The compound of Formula (8) is dissolved in an aqueous protic solvent, preferably aqueous methanol, and reacted with about 3 molar equivalents of a base, for example potassium hydroxide or lithium iodide, followed by sodium cyanide. The reaction is carried out in the temperature range from about 80°C to 120°C, preferably at about the reflux temperature of the solvent mixture, for about 8 hours. The reaction product of Formula (9) is isolated and purified by conventional means.

Step 3 - Preparation of Compounds of Formula (10)

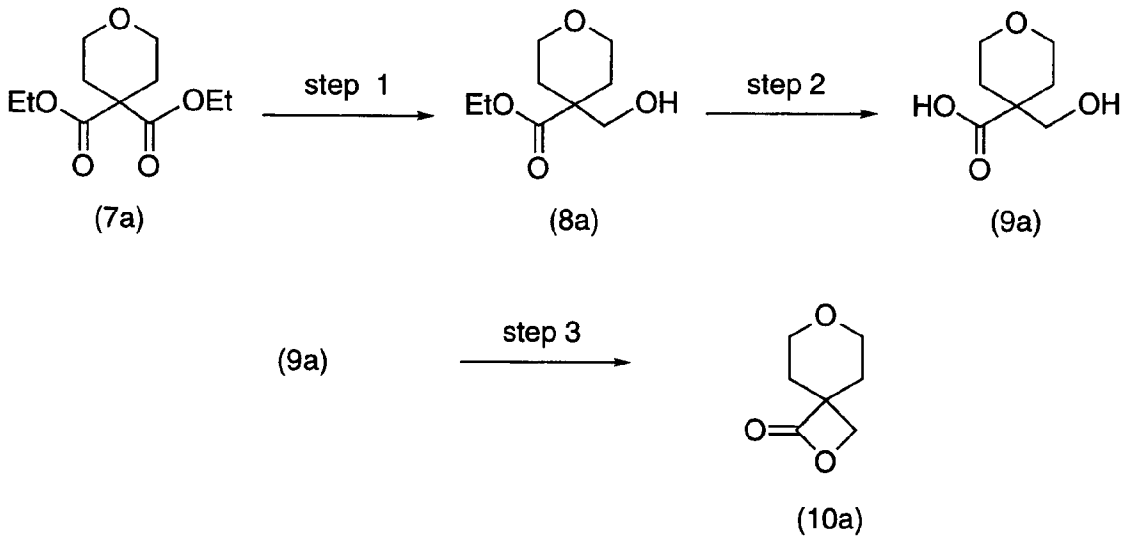
In general, the compound of Formula (9) is dehydrated to form a lactone of Formula (10).

To a mixture of the compound of Formula (9) and about 2 molar equivalents of a tertiary base, preferably triethylamine, optionally in the presence of 4-dimethylaminopyridine, in an inert solvent, for example, diethyl ether or dichloromethane, at about -20°C, is added about 1 molar equivalent of a dehydrating agent, for example trifluoromethanesulfonic anhydride, methanesulfonic anhydride, methanesulfonyl chloride, *p*-toluenesulfonyl chloride, benzenesulfonyl chloride, preferably benzenesulfonyl chloride. The reaction is carried out at about -10°C, for about 10 minutes to 4 hours, preferably about 30 minutes. The reaction product of Formula (10) is isolated by conventional means synthesis without further purification.

Preparation of Compounds of Formula (10) where R^1 and R^2 together with the Carbon to which they are attached Represent a Tetrahydropyran Derivative

To give a specific example, the preparation of a compound of Formula (10) where R^1 and R^2 together with the carbon to which they are attached represent a tetrahydropyran derivative (represented as Formula (10a)) is shown below in Reaction Scheme V, and described in Example 5.

REACTION SCHEME V

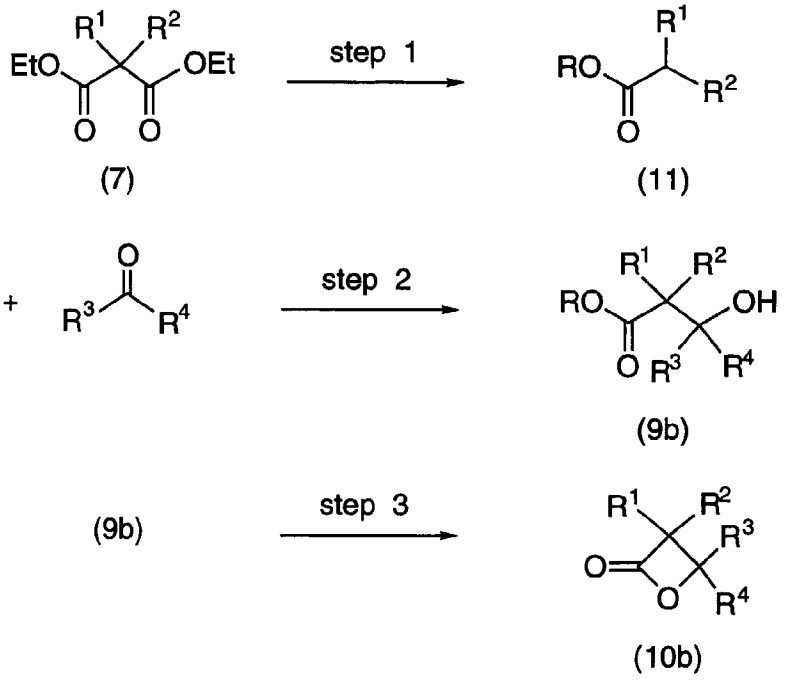


The starting compound of Formula (7a) is either commercially available or may be prepared as shown in Example 31A. Steps 1-3 are carried out in the same manner as shown in Reaction Scheme IV.

Preparation of Compounds of Formula (10) where R^3 and R^4 are as Defined in the compounds of formula I

The preparation of a compound of Formula (10) where R^3 and R^4 are as defined in the compounds of formula I, represented as Formula (10b), is shown below in Reaction Scheme VI, and described in Example 5.

REACTION SCHEME VI



Step 1 - Preparation of Compounds of Formula (11)

The compound of Formula (11), where R is Et, may be prepared from the compound of Formula (7) by decarboxylation. In general, the diester is reacted with a mixture of lithium iodide and sodium cyanide at about 130° to 140°C in a suitable solvent, for example *N, N*-dimethylformamide, for about 24 hours.

Step 2 - Preparation of Compounds of Formula (9b)

In general, an anion of a compound of Formula (11), where R is H or lower alkyl, is reacted with a compound of the formula $R^3R^4C=O$ to form a hydroxy acid or hydroxy ester, respectively, of Formula (9b).

A solution of the compound of Formula (11) in an anhydrous ethereal solvent, preferably tetrahydrofuran, is added to about 1.1 molar equivalent (when R is lower alkyl) or about 2 molar equivalents (when R is hydrogen) of a hindered base, preferably lithium diisopropylamide, in an anhydrous ethereal solvent, preferably tetrahydrofuran, at about 0°C. When the addition is complete, a small quantity of a polar solvent is optionally added, preferably hexamethylphosphoramide. To this mixture is added an excess of a compound of the formula $R^3R^4C=O$. The addition is carried out at a temperature range of about -78 to 10°C, preferably at about -78°C when R^3 and R^4 are hydrogen, or preferably 0°C for ketones, followed by reaction at room temperature for about 2-24 hours, preferably about 10 hours. Where R in the starting material of Formula (11) is hydrogen, the reaction product of Formula (9b) is isolated and purified by conventional means. Where R in the starting material of Formula (11) is lower alkyl, the reaction product of Formula (9b), where R = H, is obtained by hydrolyzing the ester product using a base, preferably lithium hydroxide, as described above, then isolating and purifying (9b) by conventional means.

Step 3 - Preparation of Compounds of Formula (10b)

The compound of Formula (9b) is then converted to a compound of Formula (10b) in the same manner as described in Reaction Scheme IV.

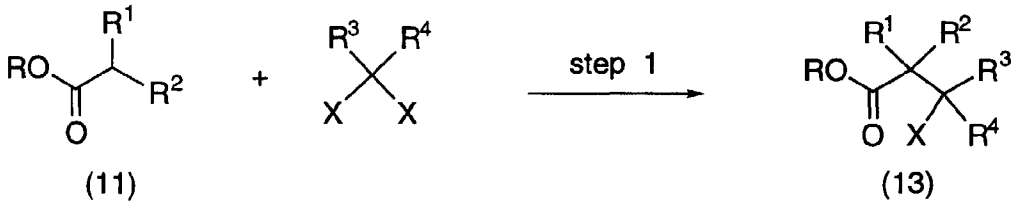
The method of Reaction Scheme VI can be used, for example, to prepare compounds of Formula (10) where R^1 and R^2 taken together with the carbon to which they are attached is tetrahydropyran-4-yl, by starting with 4-carboxytet-

rahydropyran or an ester thereof, for example, the ethyl ester. Similarly, compounds of Formula (10) where R^1 and R^2 taken together with the carbon to which they are attached is piperidin-4-yl or derivatives thereof, may be prepared by starting with 1-benzyloxycarbonyl-4-carboxypiperidine, *N*-(*tert*-butoxycarbonyl)-4-carboxypiperidine, or an ester thereof, for example, the ethyl ester.

Alternative Preparation of Compounds of Formula I

Compounds of Formula I can also be prepared from compounds of Formula (13), the preparation of which is shown below in Reaction Scheme VIa, and described in Example 5A.

REACTION SCHEME VIA



where R is hydrogen or lower alkyl, and X is halo or -*p*-tosyl.

Step 1 - Preparation of Compounds of Formula (13) from (11)

The starting compounds of Formula (13) are commercially available, for example, an ester of commercially available chloropivalic acid may be prepared conventionally, or compounds of Formula (13) may be prepared by means well known in the art, for example, Gibson and Johnson, *J. Chem. Soc.*, p2525 (1930). In general, an anion of a compound of Formula (11) is reacted with an alkyl dihalide to form a halo-substituted hydroxy acid ester of Formula (13).

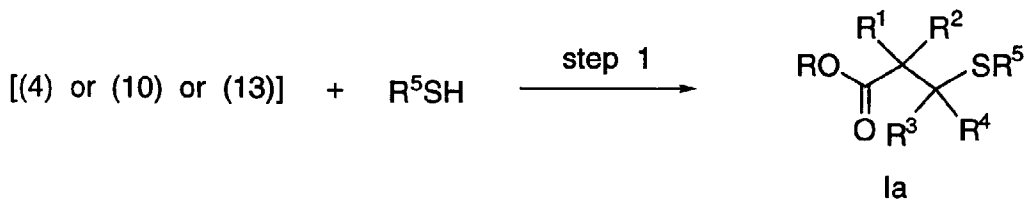
A solution of the compound of Formula (11) in an anhydrous ethereal solvent, preferably tetrahydrofuran, is added to about 1.1 molar equivalent (when R is lower alkyl) or about 2 molar equivalents (when R is hydrogen) of a hindered base, preferably lithium diisopropylamide, in an anhydrous ethereal solvent, preferably tetrahydrofuran, at about -100 to 0°C, preferably at about -78°C. To this mixture is added an excess of an alkyl dihalide, preferably diiodomethane. The addition is carried out a temperature range of about -5° to 50°C for about 1-5 hours. The reaction product of Formula (13) is isolated by conventional means, and preferably used in the next step of the synthesis without further purification.

It should be noted that a compounds of Formula (13) where X is *p*-tosyl, are obtained by tosylation by conventional means of compounds of Formula (8) or (9b).

Preparation of Compounds of Formula I

The intermediates of Formulae (4), (10), and (13) may be converted to compounds of Formula I where Y is hydroxy and n is 0, designated as compounds of Formula Ia, as shown in Reaction Scheme VII below.

REACTION SCHEME VII



where R is hydrogen or lower alkyl.

Compounds of Formula (4) are either commercially available, for example from Aldrich, or may be prepared according to methods known to those skilled in the art, for example, as described by Mannich and Rister, *Chem. Ber.*, **57,** 1116

(1924) for acids where R^3 and R^4 are each hydrogen, or may be prepared as described above, or as described in Example 3. Compounds of Formula (5) are commercially available, for example from Aldrich, Fluka, etc.), or may be prepared according to methods known to those skilled in the art, *e.g.,* as described below in Example 4.

Step 1 - Preparation of Compounds of Formula Ia from (4)

Compounds of Formula I where n is 0 and Y is hydroxy, designated as compounds of Formula Ia, may be prepared by heating an enoic acid of Formula (4) with an equimolar amount of a thiol of Formula (5) in the presence of an approximately equimolar amount of a secondary amine, preferably piperidine. The reaction is carried out in the temperature range from about 70°C to 120°C, preferably at about 100°C, for about 1 to 24 hours, preferably about 3 hours. The sulfide reaction product, a compound of Formula Ia, is isolated and purified by conventional means.

Step 1 - Preparation of Compounds of Formula Ia from (10)

Compounds of Formula I where n is 0 and Y is hydroxy, designated as compounds of Formula Ia, may be prepared by reacting a lactone of Formula (10) with about 1.1 molar equivalents of an anion of a thiol of Formula (5) (generated by reaction of (5) with an alkaline metal hydride, preferably sodium hydride in a polar solvent, preferably *N, N*-dimethylformamide). The reaction is carried out in a polar solvent, preferably *N, N*-dimethylformamide, at a temperature range of about 0°C to 70°C, preferably at about 0° to 25°C. The sulfide reaction product, a compound of Formula Ia, is isolated and purified by conventional means.

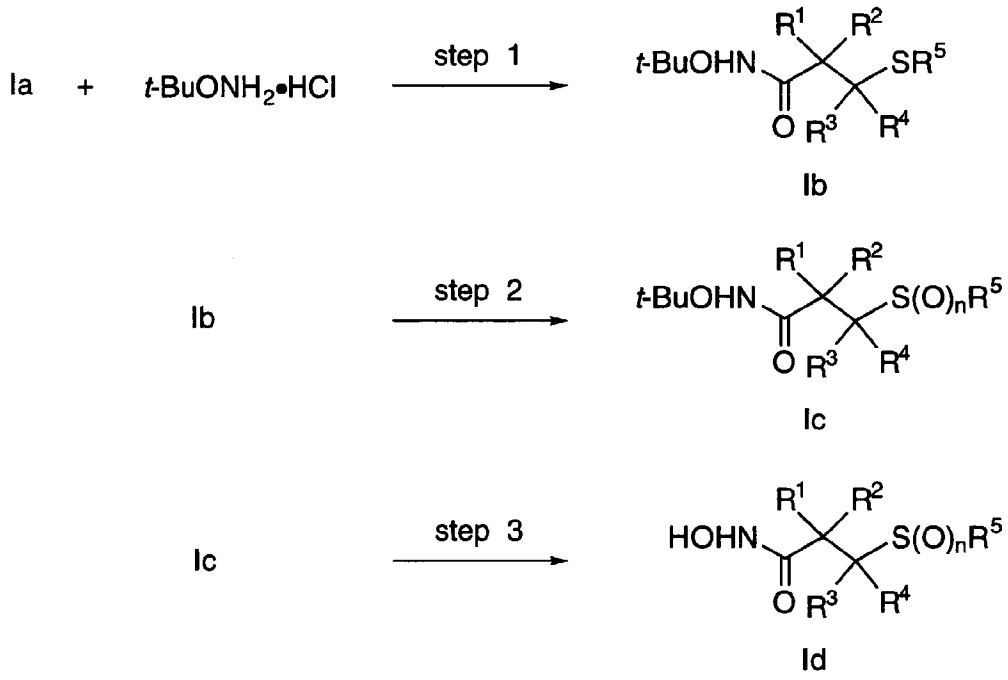
Step 1 - Preparation of Compounds of Formula Ia from (13)

Compounds of Formula I where n is 0 and Y is hydroxy or lower alkoxy, designated as compounds of Formula Ia, may be prepared by reacting an enoic acid ester of Formula (13) with about 1.1 molar equivalents of an anion of a thiol of Formula (5) (generated by reaction of (5) with an alkaline metal hydride, preferably sodium hydride in a polar solvent, preferably *N,N*-dimethylformamide). The reaction is carried out in a polar solvent, preferably *N,N*-dimethylformamide, at a temperature range of about 30°C to 120°C, preferably at about 80°C, for about 10 minutes. The sulfide reaction product, a compound of Formula Ia, is isolated and purified by conventional means.

Conversion of Compounds of Formula Ia to other Compounds of Formula I

One method of converting compounds of Formula Ia to other compounds of Formula I is shown below in Reaction Scheme VIII.

REACTION SCHEME VIII



Step 1 - Preparation of Compounds of Formula Ib

In general, compounds of Formula I where n is 0 and Y is *tert*-BuONH-, designated as compounds of Formula Ib, are prepared by reacting a compound of Formula Ia with an excess of a *O*-(*tert*-butyl)-hydroxylamine hydrochloride and *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide hydrochloride (or other carbodiimide derivatives, for example 1,3-dicyclohexylcarbodiimide), in the presence of 1-hydroxybenzotriazole hydrate and a tertiary base, for example dimethylaminopyridine, triethylamine, 4-methylmorpholine, pyridine, or a mixture of such bases. The reaction is carried out in an inert solvent, preferably methylene chloride, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 10 to 30 hours, preferably about 18 hours. The *N-tert*-butoxy reaction product, a compound of Formula Ib, is isolated and purified by conventional means.

Step 2 - Preparation of Compounds of Formula Ic where n is 1

In general, compounds of Formula I where n is 1 and Y is *tert*-BuONH-, (*i.e.,* sulfoxides), designated as compounds of Formula Ic, are prepared from compounds of Formula Ib by reaction with a mild oxidizing agent, for example sodium periodate or one equivalent of "OXONE™" (potassium peroxymonosulfate, Aldrich Chemical Co.), until starting material can no longer be detected. The reaction is carried out in an inert solvent, preferably aqueous acetone, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 10 minutes to 4 hours, preferably about 30 minutes. The sulfoxide product, a compound of Formula Ic where n is 1, is isolated and purified by conventional means.

Step 2 - Preparation of Compounds of Formula Ic where n is 2

In general, compounds of Formula I where n is 2, Y is *tert*-BuONH-, and R^1 is hydrogen (*i.e.,* sulfones), designated as compounds of Formula Ic, are prepared from compounds of Formula Ib by reaction with about 1-3 molar equivalents, preferably about 1.5 molar equivalents, of a strong oxidizing agent, for example, *m*-chloroperbenzoic acid or OXONE. The reaction is carried out in an inert solvent, preferably a protic solvent, preferably aqueous methanol, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 10 minutes to 4 hours, preferably about 2 hours. The sulfone product, a compound of Formula Ic where n is 2, is isolated and purified by conventional means.

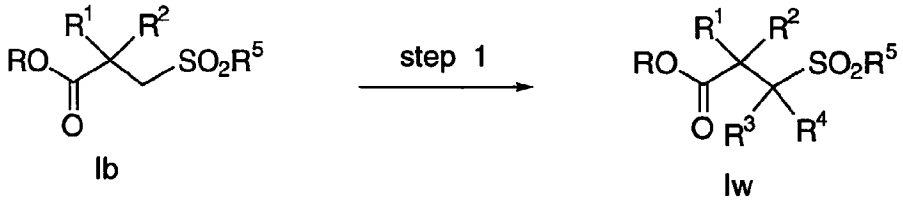
Step 3 - Preparation of Compounds of Formula Id

In general, compounds of Formula I where Y is HONH-, designated as compounds of Formula Id, are prepared by hydrolysing an *N-tert*-butoxy compound of Formula Ib or Ic under acid conditions under conditions similar to that shown for the preparation of compounds of Formula (4) above, or using hydrochloric acid gas in a sealed tube in an inert solvent, for example, 1,2-dichloroethane. The hydroxyamino reaction product, a compound of Formula Id where Y is HONH-, is isolated and purified by conventional means.

Alternative Method of Introduction of R^3 and R^4 into Compounds of Formula I

An alternative method of introducing the groups R^3 and R^4 into compounds of Formula I is shown below in Reaction Scheme VIIIA.

REACTION SCHEME VIIIA



Ib Iw

where R is hydrogen or lower alkyl.

Step 1- Preparation of Compounds of Formula I where n is 2, and R^3 is as defined in the compounds of formula I but is other than Hydrogen

The compounds of Formula I where n is 2, Y is hydroxy or alkoxy, R^3 is as defined in the compounds of formula I other than hydrogen, and R^1, R^2, and R^4 are defined in the compounds of formula I, designated as compounds of Formula Iw are prepared by the alkylation of compounds of Formula I where both R^3 and R^4 are hydrogen.

A solution of the compound of Formula Iw in an anhydrous ethereal solvent, preferably tetrahydrofuran, is added to a hindered base, preferably lithium diisopropylamide, in a manner similar shown above in Reaction Scheme VIA. To this mixture is added about 1 molar equivalent of an alkyl or aralkyl halide. The reaction addition is stirred for about 1-3 hours, then stirred stirred for an additional 1-5 hours, preferably 3 hours, at about room temperature. The reaction product is isolated and purified by conventional means.

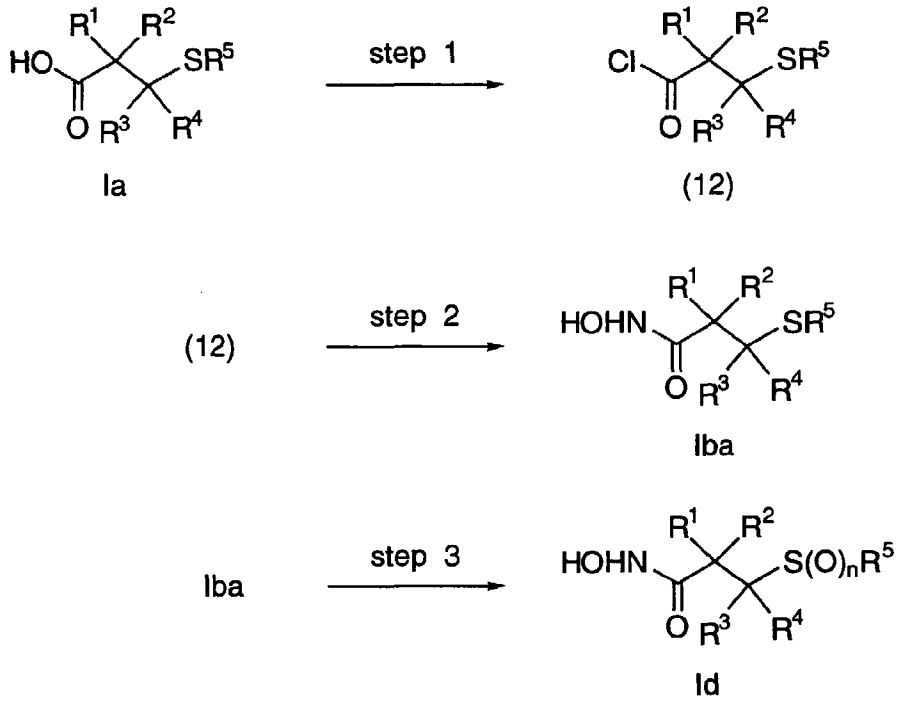
R^4 may be introduced in the same manner as shown above.

Compounds of Formula Iw can be converted to other compounds of Formula I as shown previously.

Preferred Procedure for Preparing Compounds of Formula Id from Compounds of Formula Ia

A preferred method of converting compounds of Formula Ia to other compounds of Formula I is shown below in Reaction Scheme IX.

REACTION SCHEME IX



Step 1 - Preparation of Compounds of Formula Iba

In general, an acid halide of a compound of Formula Ia, designated as compounds of Formula (12), is prepared by reacting a compound of Formula Ia with a halogenating agent.

The compound of Formula Ia is reacted with an excess of a halogenating agent, for example oxalyl chloride, oxalyl bromide, phosphorous oxychoride, phosphorous trichloride, phosphorous pentachloride, thionyl chloride, preferably oxalyl chloride in the presence of a small amount of *N, N*-dimethylformamide as a catalyst. The reaction is carried out in an inert solvent, preferably methylene chloride, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 10 to 30 hours, preferably about 18 hours. The acid halide reaction product, a compound of Formula (12), is isolated by conventional means.

Step 2 - Preparation of Compounds of Formula Iba

Compounds of Formula I where n is 0 and Y is HONH-, designated as compounds of Formula Iba, may be prepared by reacting a compound of Formula (12) with about 1-5 molar equivalents, preferably about 3.5 molar equivalents, of *N, O*-bis(trimethylsilyl)-hydroxylamine, or more preferably aqueous hydroxylamine dissolved in a suitable solvent, for example a mixture of *tert*-butanol/tetra-hydrofuran. The reaction is carried out in an inert solvent, preferably methylene chloride, in the temperature range from about 0°C to 25°C, preferably at about 25°C, for about 1-10 hours, preferably about 3 hours for *N, O*-bis(trimethylsilyl)hydroxylamine, or about 1.5 hours for aqueous hydroxylamine. The *N*-hydroxamic acid product, a compound of Formula Iba, is isolated and purified by conventional means.

Step 3 - Preparation of Compounds of Formula Id

The compound of Formula Iba is converted to a compound of Formula Id where n is 1 or 2 in the same manner as shown in Reaction Scheme VIII, steps 2 or 3, above.

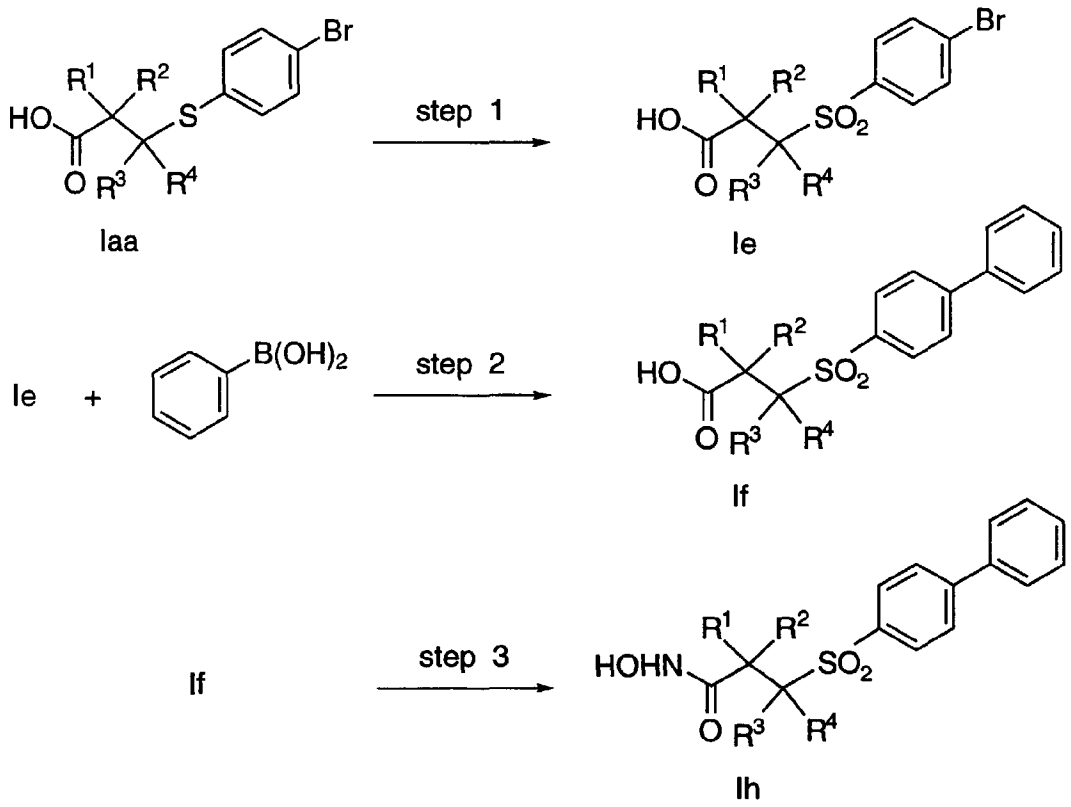
Alternative Preparation of Compounds of Formula I

It should be noted that the sequence of the steps in the above Reaction Schemes for the preparation of compounds of Formula Id may be changed. That is, a compound of Formula Ia may be oxidized first to a sulfone, followed by conversion of the carboxy group to hydroxyamino as shown above, if so desired.

Preparation of Compounds of Formula I where R^5 is Biphenyl

Compounds of Formula I where R^5 is optionally substituted biphenyl are preferably prepared from compounds of Formula Ia where R^5 is optionally substituted bromophenyl. For example, compounds where R^5 is 4-biphenyl can be prepared from compounds of Formula Ia where R^5 is 4-bromophenyl, represented below as a compound of Formula Iaa, as shown below in Reaction Scheme X.

REACTION SCHEME X



Step 1 - Preparation of Compounds of Formula Ie

In general, compounds of Formula I where n is 2, Y is hydroxy, R^5 is 4-bromophenyl, and R^1, R^2, R^3, and R^4 are as defined in the compounds of formula I, designated as compounds of Formula Ie, are prepared from compounds of Formula Iaa by reaction with a strong oxidizing agent in the same manner as shown above in Reaction Scheme VIII, Step 2.

Step 2 - Preparation of Compounds of Formula If

In general, compounds of Formula I where n is 2, Y is hydroxy, R^5 is biphenyl, and R^1, R^2, R^3, and R^4 are as defined in the compounds of formula I, designated as compounds of Formula If, are prepared by reacting a compound of Formula Ie with phenylboronic acid and zero-valent palladium catalysts, preferably tetrakis(triphenylphosphine)palladium.

The reaction is carried out in a protic solvent, preferably a mixture of ethanol and benzene, in the temperature range from about 30°C to 100°C, preferably at about 80°C. When the desired temperature is reached, aqueous 2M sodium carbonate is added, and refluxing continued for about 1-8 hours, preferably about 2 hours. The reaction product, a compound of Formula If, is isolated by conventional means and preferably purified using preparative TLC.

Step 3 - Preparation of Compounds of Formula Ih

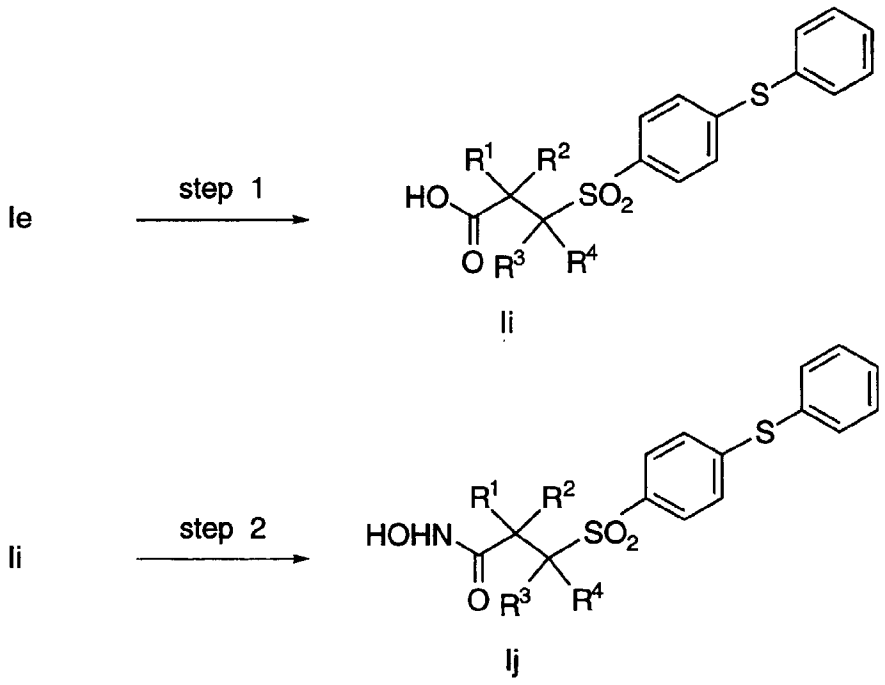
In general, compounds of Formula I where n is 2, Y is HONH-, R^5 is biphenyl, and R^1, R^2, R^3, and R^4 are as defined in the compounds of formula I, designated as compounds of Formula Ih, may be prepared from the corresponding compounds of Formula If in the same manner as shown above in Reaction Scheme VIII, or preferably as shown in Reaction Scheme IX or X.

To prepare compounds of Formula I where R^5 is substituted biphenyl, a compound of Formula Iaa optionally substituted on the 4-bromophenyl ring is reacted with an optionally substituted boronic acid in the same manner as shown above.

Preparation of Compounds of Formula I where R^5 is Diphenylsulfide

Compounds of Formula I where R^5 is optionally substituted diphenylsulfide are preferably prepared from the corresponding compounds of Formula Ie, *i.e.*, compounds of Formula I in which R^5 is optionally substituted 4-bromophenyl, prepared as in Reaction Scheme X. For example, compounds where R^5 is 4-diphenylsulfide can be prepared from compounds of Formula Ie as shown below in Reaction Scheme XI.

REACTION SCHEME XI



Step 1 - Preparation of Compounds of Formula Ii

In general, compounds of Formula I where n is 2, Y is hydroxy, R^5 is 4-diphenylsulfide, and R^1, R^2, R^3, and R^4 are as defined in the compounds of formula I, designated as compounds of Formula Ii, are prepared from compounds of Formula Ie by heating an anion of thiophenol (preferably prepared *in situ*, for example, by treatment of thiophenol with sodium or potassium hydride, preferably potassium hydride, in a polar solvent, preferably *N,N*-dimethylformamide. The

reaction is carried out in a polar solvent, preferably *N,N*-dimethylformamide, in the temperature range from about 30°C to 100°C, preferably at about 75°C, for about 4-48 hours, preferably about 18 hours. The reaction product, a compound of Formula Ii, is isolated by conventional means and preferably purified using preparative TLC.

Step 2 - Preparation of Compounds of Formula Ij

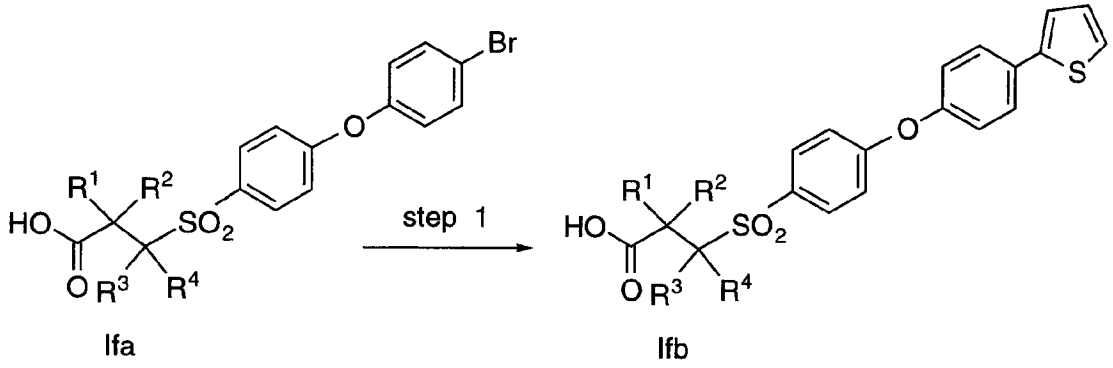
In general, compounds of Formula I where n is 2, Y is HONH-, R^5 is 4-diphenylsulfide, and R^1, R^2, R^3, and R^4 are as defined in the compounds of formula I, designated as compounds of Formula Ij, are prepared from the corresponding compounds of Formula Ii in the same manner as shown above in Reaction Scheme VIII, or preferably as shown in Reaction Scheme IX or X.

To prepare compounds of Formula I where R^5 is substituted 4-diphenylsulfide, a compound of Formula Ie optionally substituted on the 4-bromophenyl ring is reacted with an optionally substituted anion of thiophenol in the same manner as shown above.

Preparation of Compounds of Formula I where R^5 is 4-[4-(thiophen-2-yl)phenoxy]phenyl

Compounds of Formula I where R^5 is optionally substituted 4-[4-(4-thiophen-2-yl)phenoxy]phenyl are prepared from the corresponding compounds of Formula I where R^5 is optionally substituted 4-(4-bromophenoxy)phenyl. This reaction is shown in Reaction Scheme XIA.

SCHEME XIA



Ifa Ifb

Preparation of Compounds of Formula Ifb

The 4-bromo group of the compound of Formula (Ifa), which may be prepared by methods analogous to those previously shown, or as described in Example 16D, is displaced to give a compound of Formula Ifb, using the same procedure as described in Reaction Scheme X, step 2.

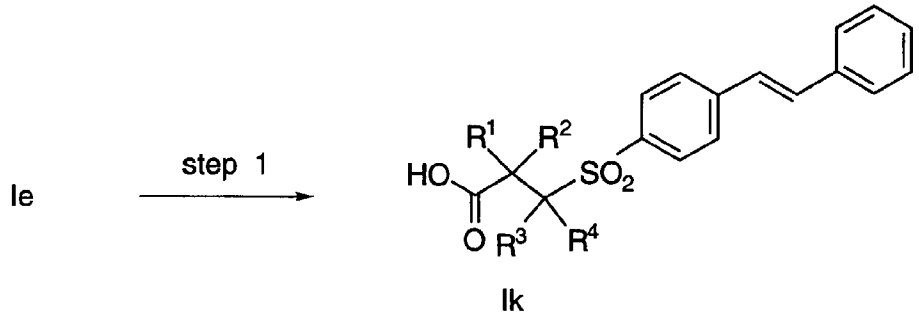
The compound of Formula (Ifa) is reacted similarly in order to introduce other aryl or heteroaryl groups.

Reduction of a compound of Formula Ifa with palladium and hydrogen replaces the bromo group by hydrogen.

Preparation of Compounds of Formula I where R^5 is 1,2-Diphenylethene

Compounds of Formula I where R^5 is optionally substituted 1,2-diphenylethene are preferably prepared from the corresponding compounds of Formula I where R^5 is optionally substituted 4-bromophenyl, as prepared in Reaction Scheme X. For example, compounds where R^5 is 4-diphenylethene can be prepared from compounds of Formula Ie as shown below in Reaction Scheme XII.

REACTION SCHEME XII



Step 1 - Preparation of Compounds of Formula Ik

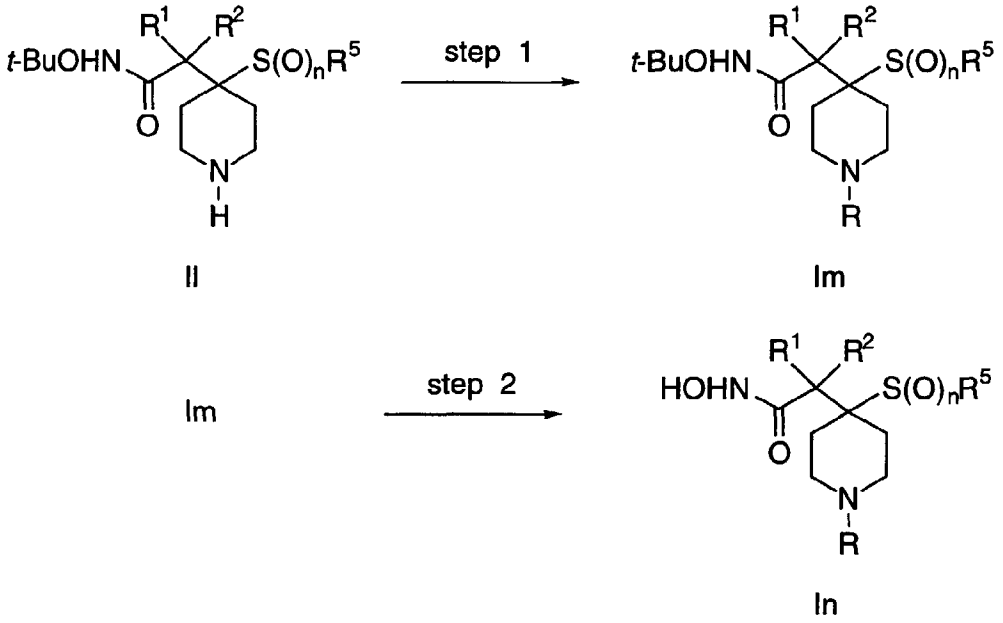
In general, compounds of Formula I where Y is hydroxy, R^5 is 4-(1,2-diphenylethene), and R^1, R^2, R^3, and R^4 are as defined in the compounds of formula I, designated as compounds of Formula Ik, are prepared by reacting a compound of Formula Ie with an optionally substituted styrene in the presence of a hindered tertiary organic base, for example diisopropylethylamine, and palladium diacetate, and trimethylphenylphosphine or other triphenylphosphine derivatives, preferably trimethylphenylphosphine or tetrakis(triphenylphosphine)-palladium(0). The reaction is carried out in the absence of solvent, in the temperature range from about 30°C to 100°C, preferably at about 80°C, for about 4-48 hours, preferably about 16 hours. The reaction product, a compound of Formula Ik, is isolated by conventional means and preferably purified using preparative TLC.

Conversion of the carboxylic acid of Formula Ik to its hydroxyamino equivalent is carried out in the same manner as shown above in Reaction Scheme VIII, or preferably as shown in Reaction Scheme IX or X.

Preparation of Compounds of Formula I where R^3 and R^4 together with the Carbon to which they are attached represent an *N*-Substituted Piperidine Derivative

The preparation of compounds of Formula I where R^1 and R^2 or R^3 and R^4 together with the carbon to which they are attached represent an *N*-substituted piperidine derivative are prepared from the corresponding unsubstituted piperidine derivative. This procedure is exemplified by reference to a compound of Formula I where R^3 and R^4 together with the carbon to which they are attached represent an *N*-substituted piperidine derivative, designated as compounds of Formula II, as shown below in Reaction Scheme XIII.

REACTION SCHEME XIII



Step 1 - Preparation of Compounds of Formula Im

Compounds of Formula I where Y is *t*-BuONH-, R^1 and R^2 are as defined in the compounds of formula I, and R^3 and R^4 together with the carbon to which they are attached represent an *N*-substituted piperidine derivative, are designated as compounds of Formula Im.

In general, compounds of Formula Im are prepared by reacting a compound of Formula II with a compound of the formula RX, where R is lower alkyl, cycloalkylalkyl, acyl, alkoxycarbonylalkyl, picolyl, $-SO_2R^a$, where R^a is lower alkyl or $-NR^bR^c$, where R^b and R^c are independently hydrogen or lower alkyl; and the like, and X is chloro, bromo or iodo; for example, RX may be methyl iodide, cyclopropylmethyl bromide, 3-picolyl chloride, ethyl bromoacetate, bromoacetamide, acetyl chloride, dimethylaminosulfonyl chloride, in the presence of a base, for example triethylamine or potassium carbonate. The reaction is carried out in a polar solvent, preferably *N,N*-dimethylformamide, in the temperature range from about 0°C to 50°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 16 hours. The reaction product, a compound of Formula Im, is isolated by conventional means and preferably used with no further purification.

Alternatively, a reductive alkylation may be carried out on a compound of Formula II to give a compound of Formula Im. For example, reducing a compound of Formula II in acetone in the presence of a catalyst, for example palladium on carbon, under hydrogen gives an *N*-isopropyl derivative of Formula Im.

Step 2 - Preparation of Compounds of Formula In

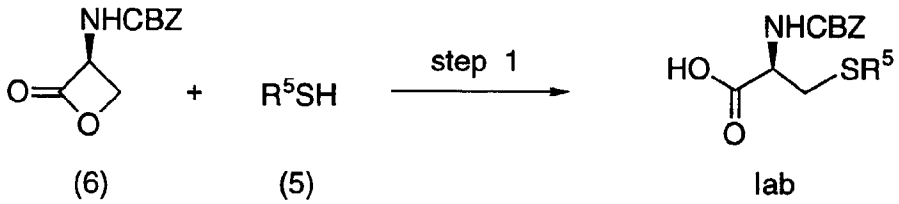
Compounds of Formula I where Y is HONH-, R^1 and R^2 are as defined in the compounds of formula I, and R^3 and R^4 together with the carbon to which they are attached represent an *N*-substituted piperidine derivative, are designated as compounds of Formula In.

In general, compounds of Formula In are prepared from a compound of Formula Im by reaction with a strong acid, preferably hydrochloric acid. The reaction is carried out in a sealed tube in an inert solvent, preferably 1,2-dichloroethane, in the temperature range from about 0°C to 45°C, preferably at about 20°C, for about 10 to 72 hours, preferably about 48 hours. The reaction product, a compound of Formula In, is isolated and purified by conventional means, preferably by chromatography.

Preparation of Compounds of Formula I where R^2 is $-NR^6R^7$

Compounds of Formula I where R^2 is $-NR^6R^7$, in which R^6 is hydrogen and R^7 is CBZ, where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are hydrogen, shown below, for example, as Formulae Ip and Iq, are prepared by a different route, as shown in Reaction Schemes XIV, XV, and XVI. This route provides compounds of Formula Iab, optically pure or as racemic mixtures, depending upon the chirality of the starting lactone.

REACTION SCHEME XIV



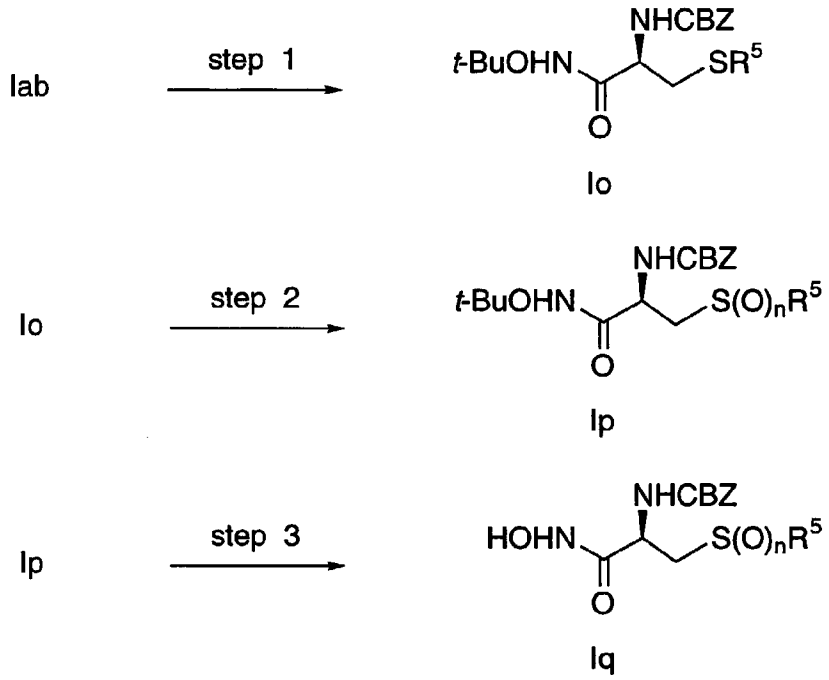
Step 1 - Preparation of Compounds of Formula Iab

In general, compounds of Formula Ia where Y is hydroxy, R^2 is $-NR^6R^7$, in which R^6 is hydrogen and R^7 is CBZ, where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are hydrogen, designated as compounds of Formula Iab, are prepared by treating an anion of a thiol of Formula (5) (preferably prepared *in situ,* for example, by treatment of Formula (5) with sodium or potassium hydride, preferably potassium hydride, in a polar solvent, preferably *N, N*-dimethylformamide) with a lactone of Formula (6). The reaction is carried out in a polar solvent, preferably *N, N*-dimethylformamide, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 5 minutes to 10 hours, preferably about 30 minutes to 6 hours. The sulfide reaction product, a compound of Formula Iab, is isolated by conventional means and preferably used directly in the next step.

Preparation of Compounds of Formula I where R^2 is $-NR^6R^7$

Compounds of Formula I where R^2 is $-NR^6R^7$, in which R^6 is hydrogen and R^7 is CBZ, where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are hydrogen, are prepared from compounds of Formula Iab as shown below in Reaction Scheme XV.

REACTION SCHEME XV



Step 1 - Preparation of Compounds of Formula Io

Compounds of Formula I where Y is *tert*-BuONH-, R^2 is -NHCBZ where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are hydrogen, designated as compounds of Formula Io, are prepared as shown in the same manner as shown in Reaction Scheme VIII, or preferably as shown in Reaction Scheme IX or X.

Step 2 - Preparation of Compounds of Formula Ip

Compounds of Formula Ip where n is 2, Y is *tert*-BuONH-, R^2 is -NHCBZ where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are hydrogen, designated as compounds of the Formula Ip, are prepared in the same manner as shown in Reaction Scheme VIII, or preferably as shown in Reaction Scheme IX or X.

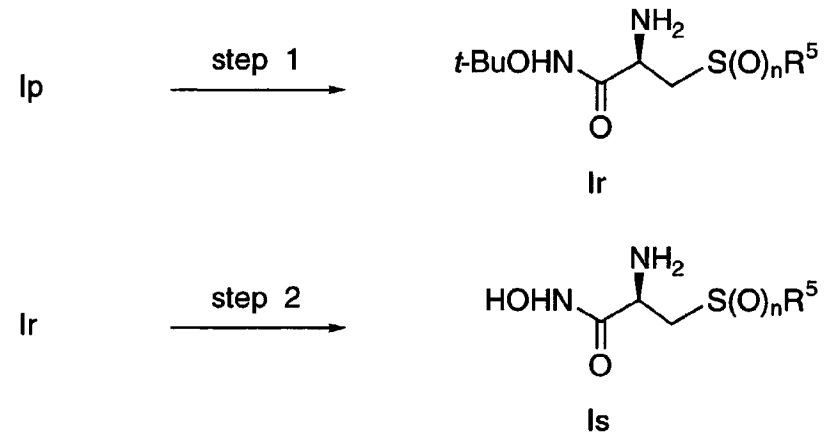
Step 3 - Preparation of Compounds of Formula Iq

Compounds of Formula I where n is 2, Y is HONH-, R^2 is -NHCBZ where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are as defined in the compounds of formula I, designated as compounds of the Formula Iq, are prepared by hydrolyzing a compound of Formula Ip in the same manner as shown above in Reaction Scheme VIII, or preferably as shown in Reaction Scheme IX or X.

Preparation of Compounds of Formula I where R^2 is $-NR^6R^7$

Compounds of Formula I where R^2 is $-NR^6R^7$, in which R^6 and R^7 are both hydrogen, and R^1, R^3 and R^4 are hydrogen, are prepared from compounds of Formula Ip as shown below in Reaction Scheme XVI.

REACTION SCHEME XVI



Step 1 - Preparation of Compounds of Formula Ir

In general, compounds of Formula I where n is 2, Y is *tert*-BuONH-, R^2 is -NH_2, and R^1 , R^3 and R^4 are hydrogen, designated as compounds of Formula Ir, are prepared by reducing a compound of Formula Ip using a metal catalyst, preferably palladium on carbon. The reaction is carried out under hydrogen at about 1 atmosphere, in a protic solvent, preferably ethanol, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 18 hours. The *N-tert*-butoxy reaction product, a compound of Formula Ir, is isolated and purified by conventional means.

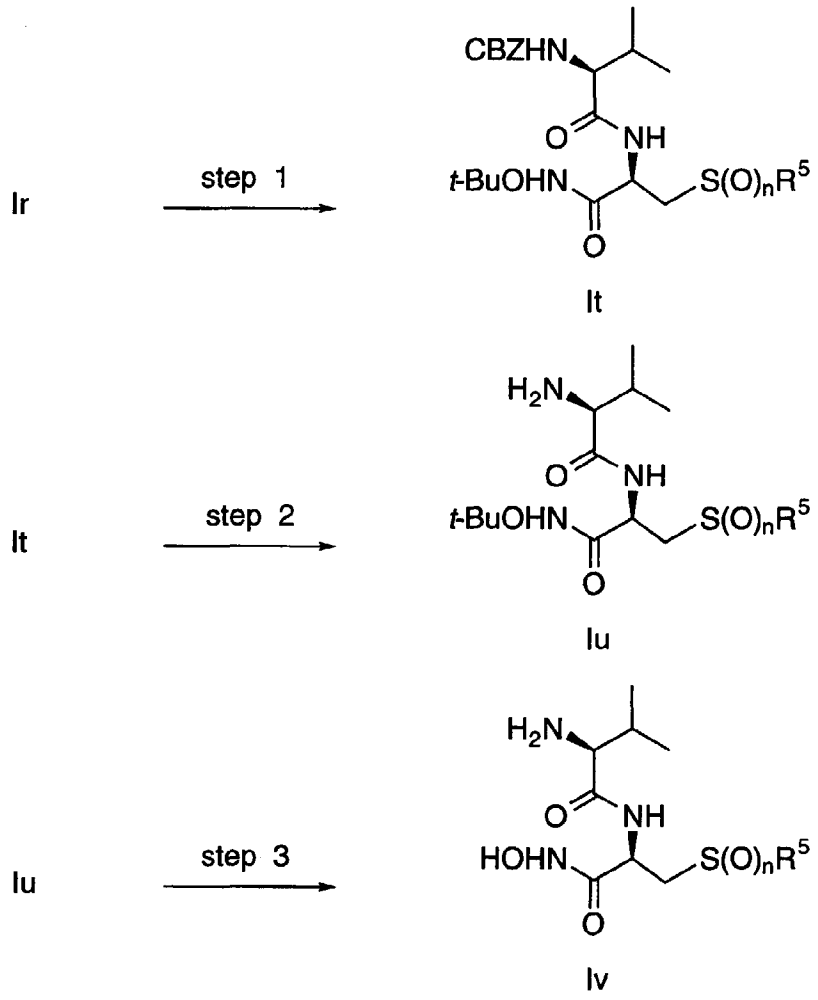
Step 2 - Preparation of Compounds of Formula Is

In general, compounds of Formula I where n is 2, Y is HONH-, R^2 is -NH_2, and R^1, R^3 and R^4 are hydrogen, designated as compounds of Formula Is, are prepared by reacting a compound of Formula Ir with a strong acid, preferably hydrochloric acid. The reaction is carried out in a sealed tube in an inert solvent, preferably 1,2-dichloroethane, in the temperature range from about -10°C to 40°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 18 hours. The hydroxyamino reaction product, a compound of Formula Is, is isolated and purified by conventional means, preferably as its hydrochloride salt.

Preparation of Compounds of Formula I where R^2 is -NR^6R^7

Alternatively, the compound of Formula Ir can be used to produce other compounds of Formula I where R^6 and/or R^7 are as defined in the Summary of the invention, but not both hydrogen. For example, the preparation of a compound of Formula I where R^2 is valine amide is shown below in Reaction Scheme XVII.

REACTION SCHEME XVII



Step 1 - Preparation of Compounds of Formula It

In general, compounds of Formula I where n is 2, Y is *tert*-BuONH-, R^2 is 2-(*S*)-CBZ-valine amide, *i.e.*, where R^6 is hydrogen and R^7 is 2-(*S*)-CBZ-3-methyl-1-butanoyl, where CBZ represents benzyloxycarbonyl, and R^1, R^3 and R^4 are hydrogen, designated as compounds of Formula It, are prepared by reacting a compound of Formula Ir with CBZ-(*S*)-valine in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide and 1-hydroxybenzotriazole and a slight excess of a tertiary amine, preferably triethylamine. The reaction is carried out in an inert solvent, preferably methylene chloride, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 6-48 hours, preferably about 16 hours. The reaction product, a compound of Formula It, is isolated by conventional means, and is preferably used in the next step without further purification.

Step 2 - Preparation of Compounds of Formula Iu

In general, compounds of Formula I where n is 2, Y is *tert*-BuONH-, R^2 is 2-(*S*)-amino-valine amide, *i.e.*, where R^6 is hydrogen and R^7 is 2-(*S*)-amino-3-methyl-1-butanoyl, and R^1, R^3 and R^4 are hydrogen, designated as compounds of Formula It, are prepared by reducing a compound of Formula It using a metal catalyst, preferably palladium on carbon. The reaction is carried out under hydrogen at about 1 atmosphere, in a protic solvent, preferably a mixture of methanol

and ethanol, in the temperature range from about 0°C to 40°C, preferably at about 25°C, for about 1 to 8 hours, preferably about 3 hours. The reaction product, a compound of Formula Iu, is isolated and purified by conventional means, preferably chromatography.

Step 3 - Preparation of Compounds of Formula Iv

In general, compounds of Formula I where n is 2, Y is HONH-, R^2 is 2-(*S*)-amino-valine amide, *i.e.,* where R^6 is hydrogen and R^7 is 2-(*S*)-amino-3-methyl-1-butanoyl, and R^1, R^3 and R^4 are hydrogen, designated as compounds of Formula Iv, are prepared by reacting a compound of Formula Iu with a strong acid, preferably hydrochloric acid. The reaction is carried out in a sealed tube in an inert solvent, preferably 1,2-dichloroethane, in the temperature range from about -20°C to 40°C, preferably at about 25°C, for about 4 to 48 hours, preferably about 24 hours. The hydroxyamine reaction product, a compound of Formula Iv, is isolated and purified by conventional means, preferably as its hydrochloride salt.

Preparation of Compounds of Formula I where R^2 is $-NR^6R^7$

In a manner similar to that shown above, compounds of Formula I where R^2 is $-NR^6R^7$, in which R^6 and R^7 are both methyl, are prepared by reacting a compound of Formula Ir in a polar solvent, preferably *N,N*-dimethylformamide, with about two equivalents of methyl iodide in the presence of a base, preferably potassium carbonate, then treating the product with hydrochloric acid gas as shown in Step 3 above.

Preparation of Compounds of Formula I where R^2 is $-NR^6R^7$

In a manner similar to that shown above, compounds of Formula I where where R^2 is $-NR^6R^7$, in which R^6 is hydrogen and R^7 is $-NHSO_2N(CH_3)_2$, are prepared by reacting a compound of Formula Ir with about one equivalent of dimethylsulfamoyl chloride in an inert solvent, preferably methylene chloride, in the presence of a base, preferably pyridine, then treating the product with hydrochloric acid gas as shown in Step 3 above.

Similarly, the compound of Formula Ir can be used to produce other compounds of Formula I where R^6 and/or R^7 are as defined in the Summary of the invention, but not both hydrogen, in the same manner as shown in Reaction Scheme XVII above.

Isolation and Purification of the Compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the Examples hereinbelow. However, other equivalent separation or isolation procedures could, of course, also be used.

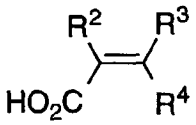
Salts of Compounds of Formula I

Some of the compounds of Formula I may be converted to a corresponding acid addition salt by virtue of the presence of basic nitrogen atoms. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained at 0° to 50°C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

In summary, the compounds of the present invention are made by the procedures outlined below:

1. A process for preparing compounds of Formula I where R^1 is hydrogen comprises:

reacting a compound of the formula:



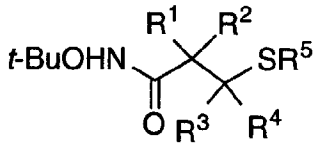
(4)

where R^2, R^3 and R^4 are as defined in the compounds of formula I, except that R^2 cannot be $-NR^6R^7$;

with a compound of the formula R^5SH, where R^5 is as defined in the compounds of formula I, in the presence of a secondary base.

2. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

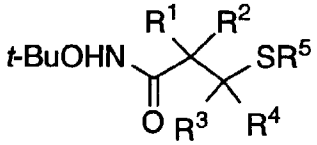


where R^1, R^2, R^3, R^4 and R^5 are as defined in the compounds of formula I,

with a mild oxidizing agent, for example, sodium periodate.

3. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

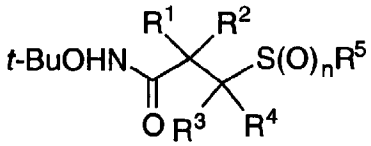


where R^1, R^2, R^3, R^4 and R^5 are as defined in the compounds of formula I,

with a strong oxidizing agent, for example, OXONE or m-chloroperbenzoic acid.

4. Alternatively, a process for preparing compounds of Formula I where n is 2 comprises:

reacting a compound of the formula:

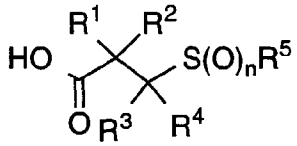


where R^1, R^2, R^3, R^4 and R^5 are as defined in the compounds of formula I,

with a strong oxidizing agent, for example, OXONE or m-chloroperbenzoic acid.

5. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

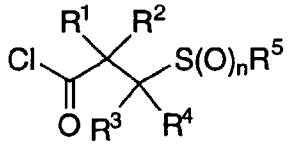


where n, R^1, R^2, R^3, R^4 and R^5 are as defined in the compounds of formula I,

with *O*-(*tert*-butyl)hydroxylamine hydrochloride in the presence of a carbodiimide, for example, *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide hydrochloride, and a tertiary amine.

6. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

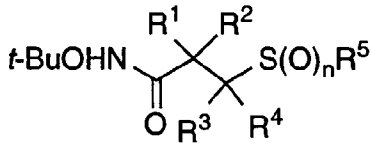


where n, R^1, R^2, R^3, R^4 and R^5 are as defined in the compounds of formula I,

with hydroxylamine or *N,O*-bistrimethylsilyl hydroxylamine.

7. Alternatively, a process for preparing compounds of Formula I comprises:

hydrolysing a compound of the formula:

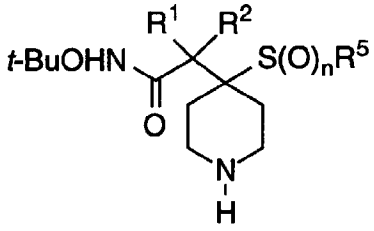


where n, R^1, R^2, R^3, R^4 and R^5 are as defined in the compounds of formula I,

under acid conditions, for example, with hydrochloric acid or trifluoroacetic acid.

8. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

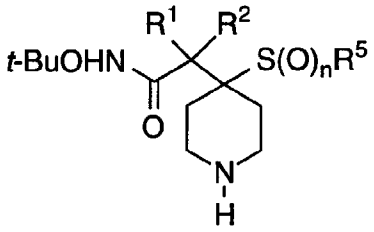


where n, R^1, R^2 and R^5 are as defined in the compounds of formula I, except that R^2 cannot be $-NR^6R^7$;

with a compound of the formula RX, where R is lower alkyl, cycloalkylalkyl, acyl, alkoxycarbonylalkyl, acetamido, picolyl, $-SO_2R^a$, where R^a is lower alkyl or NR^bR^c, where R^b and R^c are independently hydrogen or lower alkyl; and X is chloro, bromo or iodo.

9. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

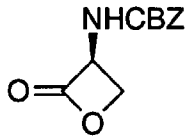


where n, R^1, R^2 and R^5 are as defined in the compounds of formula I, except that R^2 cannot be $-NR^6R^7$;

with acetone under hydrogen in the presence of a catalyst, for example, palladium on carbon, to give the *N*-isopropyl derivative.

10. Alternatively, a process for preparing compounds of Formula I comprises:

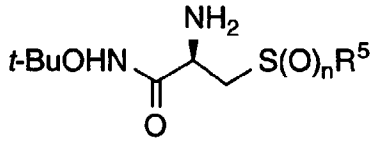
reacting a compound of the formula:



with an anion of a compound of the formula R^5 SH, where R^5 is as defined in the compounds of formula I.

11. Alternatively, a process for preparing compounds of Formula I comprises:

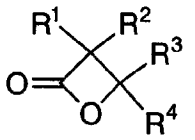
reacting a compound of the formula:



where R^5 is as defined in the compounds of formula I, with an acylating agent, for example CBZ-(*S*)-valine in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide and 1-hydroxybenzotriazole and a tertiary amine, or an alkylating agent, for example, methyl iodide in the presence of a base or a sulfamoyl halide, such as dimethylsulfamoyl chloride in the presence of a base.

12. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:

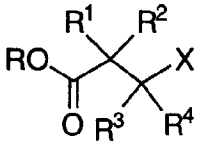


where R^1, R^2, R^3 and R^4 are as defined in the compounds of formula I, except that R^2 cannot be $-NR^6R^7$;

with a compound of the formula R^5 SH, where R^5 is as defined in the compounds of formula I, in the presence of a secondary base.

13. Alternatively, a process for preparing compounds of Formula I comprises:

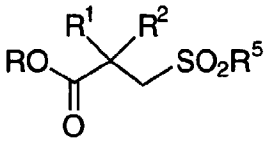
reacting a compound of the formula:



with an anion of a compound of the formula R^5SH, where R^5 is as defined in the compounds of formula I.

14. Alternatively, a process for preparing compounds of Formula I comprises:

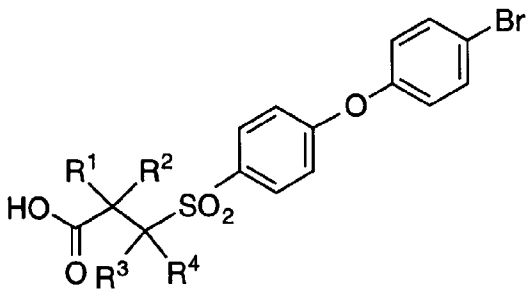
reacting a compound of the formula:



with an alkyl or aralkyl halide in the presence of a hindered base.

15. Alternatively, a process for preparing compounds of Formula I comprises:

reacting a compound of the formula:



with a compound of the formula $R^{11}B(OH)_2$ or $R^{11}SnMe_3$, where R^{11} is aryl or heteroaryl, in the presence of tetrakis(triphenylphosphine)-palladium(0).

The compounds of Formula I inhibit mammalian matrix metalloproteases, such as the stromelysins, gelatinases, matrilysin and collagenases, and are therefore useful as therapeutically active substances, especially for treating diseases associated with the MMP-induced excessive degradation of matrix and connective tissue within the mammal, for example, arthritic diseases (rheumatoid arthritis and osteoarthritis), multiple sclerosis, bone resorptive diseases (such as osteoporosis), the enhanced collagen destruction associated with diabetes, chronic obstructive pulmonary disease, cerebral hemorrhaging associated with stroke, periodontal disease, corneal ulceration, ulceration of the skin, tumor invasion and metastasis, and aberrant angiogenesis.

The compounds of Formula I substantially inhibit the release of tumor necrosis factor (TNF) from cells, and are therefore useful for the treatment of conditions mediated by TNF, for example inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, restinosis, aneurysmal disease, graft versus host reactions and autoimmune disease.

The compounds of Formula I also inhibit the release of other biologically active molecules from cells, including soluble receptors (CD30 and receptors for TNF (p55 and p75), IL-6, IL-1 and TSH), adhesion molecules (*e.g.,* L-selection, ICAM-1, fibronectin) and other growth factors and cytokines, including Fas ligand, TGF-α, EGF, HB-EGF, SCF and M-CSF. Inhibition of the release or shedding of such proteins, and are therefore useful for treating a number of disease states, for example rheumatoid arthritis, multiple sclerosis, vascular disease, Type II diabetes, HIV, cachexia, psoriasis, allergy, hepatitis, inflammatory bowel disease, and cancer.

The ability of the compounds of Formula I to inhibit matrix metalloprotease activity, such as the activity of collagenase-1, -2 and -3, stromelysin-1, gelatinases A and B, and matrilysin may be demonstrated by a variety of *in vitro* assays known to those of ordinary skill in the art, such as the assay described in the MMP Enzymatic Assay described in *FEBS,* **296**, 263 (1992) or modifications thereof. The ability of the compounds of Formula I to inhibit MMP mediated processes *in vivo* may be tested using the interleukin-1 stimulated cartilage explant assay and cartilage plug implantation assay.

The ability of the compounds of Formula I to inhibit the release of TNF as shown in Examples 45 to 47.

The present invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable non-toxic excipient and a therapeutically effective amount of a compound of formula I.

Administration of the compounds of Formula I or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a compound of Formula I as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, *etc.*

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to 75% by weight of a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease-state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of Formula I, or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients, such as for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations, and the like.

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant, such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like.

The compounds of Formula I, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, *e.g.,* polyoxyethylene glycols and polyethylene glycols (PEG), *e.g.,* PEG 1000 (96%) and PEG 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, *etc.,* a compound(s) of Formula I (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid,

sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, *etc.*

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences,* 18th Edition, Mack Publishing Company, Easton, Pennsylvania (1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, for treatment of a disease-state alleviated by the inhibition of matrix metalloprotease activity in accordance with the teachings of this invention.

The compounds of Formula I or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-state, and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.014 mg to about 14.3 mg/kg of body weight per day of a compound of Formula I or a pharmaceutically acceptable salt thereof; preferably, from about 0.07 mg to about 5 mg/kg of body weight per day; and most preferably, from about 0.14 mg to about 1.4 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 1 mg to about 1.0 gram per day of a compound of Formula I or a pharmaceutically acceptable salt thereof, preferably from about 5 mg to about 300 mg per day, and most preferably from about 10 mg to about 100 mg per day.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

Preparation of Compounds of Formula (1)

1A. Preparation of (1) where R^3 and R^4 when taken together with the Carbon to which they are attached represent *N*-CBZ-piperidine

1. A solution of benzyl chloroformate (35 ml, 247 mmol) in tetrahydrofuran (70 ml) was added to an ice-cold solution of 4-hydroxypiperidine (25 g, 247 mmol) and triethylamine (45 ml, 321 mmol) in tetrahydrofuran (350 ml). The mixture was stirred overnight at room temperature and the solvent removed under reduced pressure. The residue was partitioned between 5% hydrochloric acid and ethyl acetate, and the organic layer washed with brine, dried over magnesium sulfate, and the solvent removed under reduced pressure to give 4-hydroxy-*N*-CBZ-piperidine as a pale yellow oil.

2. Celite (66 g) was added to a solution of 4-hydroxy-*N*-CBZ-piperidine (18 g, 76.5 mmol) in methylene chloride (500 ml), followed by pyridinium chlorochromate (33 g, 153 mmol). The mixture was stirred overnight, and then isopropyl alcohol (12 ml) was added over a period of 3 hours. The reaction mixture was filtered through silica gel and the filter cake was repeatedly rinsed with methylene chloride and ethyl acetate. The combined filtrates were evaporated under reduced pressure. Silica gel chromatography using 50% ethyl acetate/hexane, gave 4-oxo-*N*-CBZ-piperidine as a yellow oil.

EXAMPLE 2

Preparation of Compounds of Formula (3)

2A. Preparation of (3) where R^2 is Hydrogen, and R^3 and R^4 when taken together with the Carbon to which they are attached represent *N*-CBZ-piperidine

tert-(Butoxycarbonylmethylene)triphenylphosphorane (28 g, 74.4 mmol) was added to 4-oxo-*N*-CBZ-piperidine (14.2 g, 61.3 mmol) in benzene (150 ml), and the solution was stirred at reflux overnight. The solution was concentrated, and the residue triturated with hexane (500 ml). Filtration and concentration of the filtrate gave 4-*tert*-butoxycarbonyl-methylene-*N*-CBZ-piperidine as a colorless oil.

2B. Preparation of (3), varying R^2, R^3, and R^4

Similarly, following the procedures of Example 2A above, but replacing 4-oxo-*N*-CBZ-piperidine with:

formaldehyde;
acetone;
propionaldehyde;
cyclopentanone;
cyclohexanone;
1,4-cyclohexanedione mono-ethylene ketal;
4-methylcyclohexanone;
phenylacetaldehyde;
4-(biphen-4-yl)butyraldehyde;
cyclopentylacetaldehyde;
tetrahydropyranone; and
tetrahydrothiopyran;

and optionally replacing *tert*-(butoxycarbonylmethylene)triphenylphosphorane with:

tert-butyl-3-phenylpropionate-2-triphenylphosphorane;
tert-butyl-propionate-2-triphenylphosphorane; and
tert-butyl-3-methylpropionate-2-triphenylphosphorane;

the following compounds of Formula (3) were prepared:

1-(*tert*-butoxycarbonyl)-1-benzylethene;
1-(*tert*-butoxycarbonyl)-2,2-dimethylethene;
1-(*tert*-butoxycarbonyl)-1-methyl-2-ethylethene;
tert-butoxycarbonylmethylenecyclopentane;
tert-butoxycarbonylmethylenecyclohexane;
tert-butoxycarbonylmethylene-4-methylcyclohexane;
1-(*tert*-butoxycarbonyl)-2-benzylethene;
1-(*tert*-butoxycarbonyl)-1-isopropyl-2-benzylethene;
1-(*tert*-butoxycarbonyl)-2-[3-(biphen-4-yl)]propylethene;
1-(*tert*-butoxycarbonyl)-2-cyclopentylmethylethene;
4-(*tert*-butoxycarbonylmethylene)-tetrahydropyran; and
4-(*tert*-butoxycarbonylmethylene)-tetrahydrothiopyran.

2C. Preparation of (3), varying R^2, R^3, and R^4

Similarly, following the procedures of Example 2A above, but optionally replacing 4-oxo-*N*-CBZ-piperidine with other compounds of Formula (1), and optionally replacing (*tert*-butoxycarbonylmethylene)triphenyl-phosphorane with other compounds of Formula (2), other compounds of Formula (3) are prepared.

EXAMPLE 3

Preparation of Compounds of Formula (4)

3A. Preparation of (4) where R^2 is Hydrogen, and R^3 and R^4 when taken together with the Carbon to which they are attached represent *N*-CBZ-piperidine, a Compound of Formula (4a)

Trifluoroacetic acid (10 ml) was added to 4-*tert*-butoxycarbonylmethylene-*N*-CBZ-piperidine (20 g, 60.3 mmol) in methylene chloride (30 ml) and the solution was stirred at room temperature for 1.5 hours. After evaporation of the solvent, the residue was triturated with diethyl ether to give 4-carboxymethylene-*N*-CBZ-piperidine as a crystalline white solid.

3B. Preparation of (4) where R^2 is Hydrogen, and R^3 and R^4 when taken together with the Carbon to which they are attached represent Tetrahydropyran, a Compound of Formula (4b)

Methanol (204 ml) was slowly added to a suspension of sodium hydride (5.48 g, 228.2 mmol) in tetrahydrofuran (204 ml) at 0°C. When addition was complete, trimethylphosphonoacetate (34.22 ml, 211.4 mmol) was added to the mixture at such a rate as to maintain the temperature below 12°C. Stirring was continued for a further 10 minutes. To this reaction mixture was added a solution of 2,3,5,6-tetrahydropyran-4-one (16.28 g, 163.0 mmol) in tetrahydrofuran

(20 ml), keeping the temperature below 30°C. After the addition was complete, stirring was continued for 30 minutes at room temperature, then methanol (100 ml) and 2M sodium hydroxide (326 ml) was added, and the mixture stirred overnight at room temperature. The resulting solution was concentrated to one half of the original volume, and acidified to pH 1.2 with 6M hydrochloric acid (108 ml). The reaction mixture was partitioned between ethyl acetate and water, the combined organic extracts dried over magnesium sulfate, and solvent removed under reduced pressure to give 4-(carboxymethylene)-2,3,5,6-tetrahydropyran (22.62 g), which was used with no further purification.

3C. Preparation of (4), varying R^2, R^3, and R^4

Similarly, following the procedures of Example 3A above, but replacing 4-(*tert*-butoxycarbonylmethylene)-*N*-CBZ-piperidine with other compounds of Formula (3), the following compounds of Formula (4) were prepared:

1-benzyl-1-carboxyethene;
1-carboxy-2,2-dimethylethene;
1-carboxy-2-ethyl-1-methylethene;
carboxymethylenecyclopentane;
carboxymethylenecyclohexane;
carboxymethylene-(4-methylcyclohexane);
4-carboxymethylenecyclohexanone mono-ethylene ketal;
2-benzyl-1-carboxyethene;
2-[3-(biphen-4-yl)propyl]-1-carboxyethene;
2-benzyl-1-carboxy-1-isopropylethene;
1-carboxy-2-cyclopentylmethylethene;
4-carboxymethylene-tetrahydrothiopyran; and
4-carboxymethylene-(tetrahydrothiopyran-1,1-dioxide).

3D. Preparation of (4), varying R^2, R^3, and R^4

Similarly, following the procedures of Example 3A above, but replacing 4-(*tert*-butoxycarbonylmethylene)-*N*-CBZ-piperidine with other compounds of Formula (3), other compounds of Formula (4) are prepared, or may be prepared by means well known to those skilled in the art. Alternatively, they are commercially available, for example, 1-cyclopentene carboxylic acid and 1-cyclohexene carboxylic acid are available from Lancaster Synthesis Inc.

EXAMPLE 4

Preparation of Compounds of Formula (5)

4A. Preparation of (5) where R^5 is 4-Phenoxyphenyl

A solution of sodium thiomethoxide (25 g) and 4-bromodiphenyl ether (25 g) in *N,N*-dimethylformamide (DMF) (150 ml) was refluxed overnight. The mixture was cooled and added to dilute aqueous sodium hydroxide. The water layer was washed with ether to remove by-products and acidified with hydrochloric acid. The product, 4-(phenoxy)thiophenol, was extracted with ether, and the ether layer dried and evaporated to give 4-(phenoxy)thio-phenol (19-20 g) as a red oil. This material can be used without further purification.

4B. Alternative Preparation of (5) where R^5 is 4-(4-Bromophenoxy)phenyl

A solution of 4-bromodiphenyl ether (50 g, 200.7 mmol) in methylene chloride (118 ml) was cooled to 0°C and chlorosulfonic acid (14.7 ml, 220.8 mmol) was added dropwise over a 20 minute period. The solution was stirred an additional 10 minutes, warmed to room temperature and stirred an additional 1 hour. To this mixture was added oxalyl chloride (23.6 ml, 270.9 mmol), followed by *N,N*-dimethylformamide (1.5 ml) as a catalyst, and the mixture refluxed for 2 hours. The mixture was cooled to room temperature, and additional oxalyl chloride (23.6 ml, 270.9 mmol) was added, the mixture refluxed for 3 hours, cooled to room temperature and stirred 12 hours more. The solution was concentrated to an oil, azeotroped several times using methylene chloride and put under high vacuum (1 torr) for several hours until the mixture had completely solidified. This mixture was immediately dissolved in methylene chloride (160 ml) which was added dropwise to a solution of triphenylphosphine (157.0 g, 602 mmol) in methylene chloride (160 ml) containing *N,N*-dimethylformamide (4 ml, 52.2 mmol). The mixture was stirred 2 hours, diluted with 1M aqueous hydrochloric acid (300 ml) and stirred for 1 hour. The aqueous layer was separated, extracted with methylene chloride (200 ml), and the organic layers were combined, washed with 200 ml of brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting

solid was further purified through trituration with 750 ml of hexane. The solid was then dissolved in 750 ml of diethyl ether, extracted with 2M aqueous sodium hydroxide (2 x 350 ml), and the basic aqueous layer back extracted using diethyl ether (2 x 400 ml). The aqueous layer was adjusted to pH 2, extracted with diethyl ether (3 x 200 ml) and the combined organic layers dried ($MgSO_4$) and concentrated to afford 4-(4-bromophenoxy)thiophenol (45.6 g, 81%). ^{1}HNMR ($CDCl_3$) δ 3.43 (s, 1H), 6.86 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H).

The corresponding 4-chloro and 4-fluoro analogues were obtained in similar fashion from the corresponding commercially available 4-halodiphenylethers, respectively.

4-(4-chlorophenoxy)thiophenol: ^{1}HNMR ($CDCl_3$) δ 3.43 (s, 1H), 6.90 (m_c, 4H), 7.27 (m_c, 4H).

4-(4-fluorophenoxy)thiophenol: ^{1}HNMR ($CDCl_3$) δ 3.41 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.00 (m_c, 4H), 7.26 (d, J = 8.7 Hz, 2H).

4-(4-pyridyloxy)thiophenol: ^{1}HNMR ($CDCl_3$) δ 7.05 (d, J =9.0 Hz, 2H), 7.29 (d, J = 7.3 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 8.70 (d, J = 7.3 Hz, 2H); EIMS (M^+): 203.

4-(5-chloro-2-pyridyloxy)thiophenol: ^{1}HNMR ($CDCl_3$) δ 6.87 (d, J =8.5 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 2.8 Hz, 1H).

EXAMPLE 5

Preparation of Compounds of Formula (10)

5A. Preparation of a Compound of Formula (8) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran, a Compound of Formula (8a)

A solution of 1.5M diisobutylaluminum hydride (DIBAL-H) (419 ml, 629 mmol) in toluene was added to a 3-L Morton flask equipped with a nitrogen gas inlet, mechanical stirrer, low temperature thermometer, 500 ml pressure equalizing funnel, and containing tetrahydropyran-4,4-dicarboxylic acid diethyl ester (70.78 g, 307.4 mmol) in toluene (600 ml) at -40°C, at a rate to maintain an internal temperature no higher than -25°C. The mixture was stirred an additional 10 minutes and anhydrous ethanol (595 ml) was added dropwise over 20 minutes maintaining an internal temperature no higher than -15°C. Solid sodium borohydride (11.6 g, 307.4 mmol) was added in three portions over a 15 minute period, the cooling bath was removed, the mixture allowed to warm to room temperature over 1 hour, and saturated aqueous sodium sulfate (325 ml) added over 15 minutes. The mixture was cooled to -15°C, ethyl acetate (250 ml) was added, and the flocculent white precipitate filtered over a pad of celite. The celite pad was washed with ethyl acetate (7 x 450 ml), the filtrate washed with brine (200 ml), dried over magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in the minimum amount of ethyl acetate, filtered through a sintered glass funnel containing silica gel (40 g), eluting with ethyl acetate, and the filtrate concentrated *in vacuo* to afford the hydroxyester, 4-(hydroxymethyl)tetrahydropyran-4-carboxylic acid ethyl ester, as a pale yellow oil (48.5 g, 84%).

5B. Alternative Preparation of a Compound of Formula (8) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran

1. To a solution of tetrahydropyran-4,4-dicarboxylic acid diethyl ester (400 mg, 1.74 mmol) in *N,N*-dimethylformamide (4 ml), was added lithium iodide (1.16 g, 8.66 mmol), followed by sodium cyanide (94 mg, 1.91 mmol). The mixture was heated at 130°C for 7 hours, 140°C for 25 hours, after which GC analysis indicated the reaction to be >95% complete. The mixture was partitioned between 33% diethyl ether/hexanes (100 ml) and brine (25 ml). The organic layer was washed with additional brine (25 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the tetrahydropyran-4-carboxylic acid ethyl ester (253 mg, 92%). Note: Substitution of 2 equivalents of sodium acetate for 1.1 equivalents of sodium cyanide in this reaction and heating 12 hours longer provides identical results.

2. Lithium diisopropylamide was prepared by the addition of 2.5M *N*-butyl lithium (30.3 ml, 75.6 mmol) in hexanes to a solution of diisopropylamine (10.6 ml, 75.6 mmmol) in tetrahydrofuran (244 ml) at 0°C and stirring for 20 minutes. Then a solution of tetrahydropyran-4-carboxylic acid ethyl ester (10 g, 63.2 mmol) in tetrahydrofuran (50 ml) was added to the solution of lithium diisopropylamide over 15 minutes at -78°C. The resulting solution was stirred an additional 50 minutes, and solid paraformaldehyde (10 g) was added in one portion. The mixture was slowly allowed to warm to room temperature over 9 hours, diluted with 2M aqueous hydrochloric acid (100 ml), and filtered over a pad of celite pad which was washed with diethyl ether (2 x 200 ml). The aqueous layer of the filtrate was washed with additional portions of diethyl ether (2 x 200 ml). The combined organic layers were washed once with 2M aqueous hydrochloric acid (100 ml), saturated aqueous sodium bicarbonate (100 ml), dried over magnesium sulfate, and concentrated *in vacuo* to afford a slightly impure product 4-(hydroxymethyl)tetrahydropyran-4-carbox-

ylic acid ethyl ester (11.5 g, 97%), which was taken into the next reaction without further purification. IR (neat) 3433 (br), 1726 cm-^{1}; ^{1}HNMR ($CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.57 (ddd, *J* = 13.8, 10.1, 4.4 Hz, 2H), 2.07 (dm, *J* = 13.8 Hz, 2H), 2.30-2.45 (br s, 1H), 3.56 (ddd, *J* = 11.9, 10.3, 2.7 Hz, 2H), 3.66 (s, 2H), 3.82 (dt, *J* = 11.9, 4.2 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 14.25 (q), 30.54 (t), 46.63 (s), 61.04 (t), 64.79 (t), 69.02 (t), 175.24 (s); HRMS Calcd for $C_9H_{16}O_4$: 188.1049. Found: 188.1053.

5C. Preparation of a Compound of Formula (8) where R^1 and R^2 taken together with the Carbon to which they are attached represent Piperidine. a Compound of Formula (8)

Lithium diisopropylamide was prepared by the addition of 1.6M *N*-butyl lithium (29.1 ml, 46.6 mmol) in hexanes to a solution diisopropylamine (6.5 ml, 46.6 mmmol) in tetrahydrofuran (150 ml) at 0°C with stirring for 20 minutes at -78°C. Then a solution of neat *N*-(*tert*-butoxycarbonyl)-piperidine-4-carboxylic acid ethyl ester (10 g, 38.9 mmol) was added over 5 minutes, and the resulting solution was stirred an additional 50 minutes. Solid paraformaldehyde (13.5 g, 155.4 mmol) was added in one portion, and the mixture slowly allowed to warm to room temperature over 9 hours. The mixture was diluted with 2M aqueous hydrochloric acid (100 ml), filtered over a pad of celite, washed with diethyl ether (2 x 200 ml). The combined organic layers were washed once with 2M aqueous hydrochloric acid (100 ml), saturated aqueous sodium bicarbonate (100 ml), dried over magnesium sulfate, and concentrated *in vacuo.* Chromatography on silica gel, and eluting with 50% ethyl acetate/hexanes, yielded slightly impure *N*-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)piperidine-4-carboxylic acid ethyl ester (10.57 g, 95%) as a pale yellow oil which was taken immediately into the hydrolysis reaction (LiOH): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.4 Hz, 3H), 1.40-1.53 (m, 2H), 1.46 (s, 9H), 2.00-2.12 (m, 2H), 3.05-3.16 (m, 2H), 3.65 (s, 2H), 3.70-3.83 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H).

5D. Preparation of a Compound of Formula (9) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran, a Compound of Formula (9a)

Lithium hydroxide monohydrate (16.7 g, 398.5 mmol) was added to a solution of 4-(hydroxymethyl)tetrahydropyran-4-carboxylic acid ethyl ester (25.0 g, 132.8 mmol) in 4.5:1 methanol/water (220 ml). The mixture was heated to reflux for 40 minutes and the methanol removed *in vacuo* by concentration using a bath temperature no higher than 45°C. The aqueous layer was then extracted into diethyl ether (4 x 100 ml) and the combined ether layers washed twice with 2M sodium hydroxide (15 ml). The combined aqueous base layers were cooled to 0°C, acidified to pH 3.0 with 8M aqueous hydrochloric acid, saturated with solid sodium chloride and extracted with ethyl acetate (8 x 250 ml). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo.* The white fluffy powder residue was recrystallized from the minimum amount of methylene chloride/hexanes to afford pure 4-(hydroxymethyl)tetrahydropyran-4-carboxylic acid (17.05 g, 80%).

5E. Alternative Preparation of a Compound of Formula (9) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran

Lithium diisopropylamide was prepared by the addition of 2.45M *N*-butyl lithium (16.5 ml) in hexanes to a solution diisopropylamine (5.80 ml, 41.4 mmmol) in tetrahydrofuran (40 ml) at 0°C with stirring for 20 minutes. Then a solution of tetrahydropyran-4-carboxylic acid (2.5 g, 19.2 mmol) in tetrahydrofuran (10 ml) was added to the solution of lithium diisopropylamide over 15 minutes to form a slurry, followed by hexamethylphosphoramide (2 ml). The resulting solution was stirred for 25 minutes, then immediately warmed to room temperature after a stream of gaseous formaldehyde (prepared by heating 4 g of paraformaldehyde at 175-200°C over 5-10 minutes) was passed through the solution. The slurry was carefully concentrated at ambient temperature, acidified to pH 3 with 8M hydrochloric acid, saturated with solid sodium chloride, and extracted with ethyl acetate (8 x 100 ml). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo.* Chromatography over silica gel (80 g), and eluting with 10% methanol/methylene chloride, yielded 4-(hydroxymethyl)tetrahydropyran-4-carboxylic acid as a white solid (1.80 g, 58%). mp 113.7-115°C; IR (KBr) 3420 (br), 1724 cm-^{1}, ^{1}HNMR (DMSO-d_6) δ 1.43 (ddd, *J* = 13.5, 11.0,4.4 Hz, 2H), 1.85 (dm, *J* = 13.4 Hz, 2H), 3.37 (td, *J* = 11.3, 3.0 Hz, 2H), 3.43 (s, 2H), 3.71 (dt, *J* = 11.6, 3.9 Hz, 2H), 4.81 (br, s, 1H); 12.24 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 30.42 (t), 46.38 (s), 64.35 (t), 68.15 (t), 69.02 (t), 176.08 (s); HRMS Calcd. for $C_7H_{12}O_4$: 160.0735. Found: 160.0731. Anal. Calcd. for $C_7H_{12}O_3$: C, 52.49; H, 7.55. Found: C, 52.50; H, 7.62.

5F. Preparation of a Compound of Formula (9) where R^1 and R^2 taken together with the Carbon to which they are attached represent Piperidine. a Compound of Formula (9b)

Lithium hydroxide monohydrate (6.95 g, 165.6 mmol) was added to solution of *N*-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)piperidine-4-carboxylic acid ethyl ester (9.52 g, 33.1 mmol) in 2:1 methanol/water (100 ml). The mixture was heated to reflux for 30 minutes, the methanol removed *in vacuo* by concentration using a bath temperature no

higher than 45°C. The aqueous layer was cooled to 0°C, acidified to pH 3.0 using 6M aqueous hydrochloric acid, and extracted with ethyl acetate (4 x 75 ml). The combined organic layers were dried over magnesium sultate, and concentrated *in vacuo*, and recrystallized from dichloromethane/hexanes to afford *N*-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)piperidine-4-carboxylic acid (8.59 g, 100%).

5G. Alternative Preparation of a Compound of Formula (9) where R^1 and R^2 taken together with the Carbon to which they are attached represent Piperidine

Lithium diisopropylamide was prepared by the addition of 2.45M *N*-butyllithium (69 ml, 168.8 mmol) in hexanes to a solution diisopropylamine (24 ml, 171.2 mmmol) in tetrahydrofuran (40 ml) at 0°C with stirring for 20 minutes. Then a solution of *N*-(*tert*-butoxycarbonyl)-piperidine-4-carboxylic acid (18 g, 78.5 mmol) in tetrahydrofuran (35 ml) was added to the solution of lithium diisopropylamide over 15 minutes to form a slurry, followed by hexamethylphosphoramide (2 ml). The resulting solution was stirred for 25 minutes, then stream of gaseous formaldehyde (prepared by heating paraformaldehyde (16.4 g, 189 mmol) at 175-200°C over 5-10 minutes) was passed through the solution, which was allowed to immediately warm to room temperature. The slurry was concentrated at ambient temperature, acidified to pH 4 with 6M hydrochloric acid, saturated with solid sodium chloride, and extracted with ethyl acetate (8 x 100 ml). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*. Chromatography over silica gel, and eluting with 1% methanol/ methylene chloride, afforded *N*-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)piperidine-4-carboxylic acid as a white solid (4 g, 20%). mp 156.6-157.3 °C; ^{1}HNMR (DMSO-d_6) δ 1.25-1.37 (m, 2H), 1.38 (s, 9H), 1.85 (dm, J = 13.7 Hz, 2H), 2.78-2.94 (br m, 2H), 3.41 (s, 1H), 3.70 (dm, J = 12.8 Hz, 2H), 4.87 (br s, 1H), 12.34 (s, 1H); Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.72; H, 8.10; N, 5.53.

5H. Preparation of (10) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran a Compound of Formula (10a)

Trifluoromethanesulfonic anhydride (11.1 ml, 66.2 mmol), followed by triethylamine (17.8 ml, 127.4 mmol) was added to a slurry of 4-(hydroxymethyl)tetrahydropyran-4-carboxylic acid (10.20 g, 63.68 mmol) in anhydrous diethyl ether cooled to 0°C (115 ml). The biphasic solution was stirred for 20 hours, warmed to room temperature, stirred an additional 2 hours. The layers were separated by decantation, and the lower layer diluted with 2% aqueous sodium bicarbonate solution (50 ml) and extracted with methylene chloride (4 x 200 ml). The combined organic extracts were washed with additional 2% aqueous sodium bicarbonate (100 ml), dried over magnesium sulfate, and concentrated *in vacuo* to afford 2,7-dioxa-spiro[3.5]nonane-1-one as a pale yellow oil (10.8 g). IR (KBr) 1821 cm^{-1}; ^{1}HNMR (CD_3Cl_3) δ 1.92 (ddd, J = 13.4, 8.1, 4.0 Hz, 2H), 2.10 (dddd, J = 13.4, 6.1,3.4, 0.8 Hz, 2H), 3.70 (ddd, J = 11.8, 6.3, 3.9 Hz, 2H), 3.92 (ddd, J = 11.8, 7.9, 3.4 Hz, 2H), 4.15 (s, 2H); ^{13}CNMR (CD_3Cl_3) δ 30.78 (t), 55.78 (s), 64,46 (t), 71.50 (t), 173.42 (s), MS(EI) m/e=142. MS(CI) M+ =H m/e=143, M+ +HNH_4 m/e=160.

5I. Preparation of a Compound of Formula (10) where R^1 and R^2 taken together with the Carbon to which they are attached represent Piperidine, a Compound of Formula (10b)

Trifluoromethanesulfonic anhydride (2.60 ml, 15.39 mmol), followed by triethylamine (4.30 ml, 30.78 mmol) was added to a slurry of *N*-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine-4-carboxylic acid (3.80 g, 14.65 mmol) in anhydrous diethyl ether (27 ml) cooled to 0°C. The biphasic solution was stirred for 23 hours, warmed to room temperature, stirred an addition 1 hour, and the upper diethyl ether layer separated by decantation. The lower was extracted with additional portions of diethyl ether (2 x 100 ml), and the combined organic extracts washed with aqueous sodium bicarbonate solution (2 x 50 ml), dried over magnesium sulfate, and concentrated *in vacuo* to afford 7-(butoxycarbonyl)-2-oxa-7-azaspiro[3.5]nonan-1-one as a pale yellow oil (2.88 g, 82%). ^{1}HNMR ($CDCl_3$) δ 1.48 (s, 9H), 1.79-1.89 (m, 2H), 2.02-2.10 (m, 2H), 3.48-3.66 (m, 4H), 4.13 (s, 2H).

EXAMPLE 6

Preparation of a Compound of Formula (13)

6A. Preparation of (13) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran, and X is Iodo

Lithium diisopropylamide was prepared by the addition of 2.5M *N*-butyl lithium (5.6 ml, 13.9 mmol) in hexanes to a solution of diisopropylamine (1.95 ml, 13.9 mmmol) in tetrahydrofuran (30 ml) at 0°C with stirring for 20 minutes. Then a solution of tetrahydropyran-4-carboxylic acid ethyl ester (2 g, 12.7 mmol) in tetrahydrofuran (8 ml) was added to the solution of lithium diisopropylamide at a temperature of -78°C over 15 minutes. The resulting solution was stirred an

additional 50 minutes, and diiodomethane (1.14ml, 14.2 mmol) was added. The resulting mixture was stirred an additional 50 minutes, warmed to room temperature over 30 minutes, then recooled to 0°C. The mixture was diluted with 1M aqueous hydrochloric acid (25 ml), extracted with diethyl ether (2 x 100 ml), and washed with additional portions of diethyl ether (2 x 50 ml). The combined organic layers were washed once with 1M aqueous hydrochloric acid (100 ml), saturated aqueous sodium bisulfite (100 ml), saturated aqueous sodium bicarbonate (100 ml), and dried over magnesium sulfate, and concentrated *in vacuo*. The residue was filtered over a plug of silica gel, eluting successively with hexanes and ethyl acetate, removing excess alkylating agent with the hexane wash, to afford pure 4-(iodomethyl)tetrahydropyran-4-carboxylic acid ethyl ester as a pale yellow oil which was taken directly into the next reaction without further purification (3.20 g, 85%). IR (KBr) 1732 cm^{-1}; ^{1}HNMR ($CDCl_3$) 1.31 (q, J = 7.3 Hz, 3H), 1.56 (ddd, J = 14.6, 10.9, 4.5, 2H), 2.17 (ddd, J = 14.6, 5.7, 3.3, 2H), 3.31 (s, 2H), 3.51 (ddd, J = 11.7, 11.1, 2.5 Hz, 2H), 3.51 (td, J = 11.7, 4.3 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 14.33 (q), 15.04 (t), 34.70 (t), 45.26 (s), 61.34 (t), 65.22 (t), 172.89 (s); EIHRMS Calcd. for $C_9H_{15}IO_3$ (M^+): 298.0066. Found: 298.0066. Anal. Calcd. for $C_9H_{15}IO_3$: C, 36.26; H, 5.07. Found: C, 36.56; H, 5.09.

6B. Preparation of (13) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran, and Varying X

Similarly, replacing diiodomethane with dibromomethane or bromochloromethane, the following compounds of Formula (13) were prepared:

4-(bromomethyl)tetrahydropyran-4-carboxylic acid ethyl ester: IR (neat) 1732 cm^{-1}; ^{1}HNMR ($CDCl_3$) 1.30 (q, J = 7.1 Hz, 3H), 1.59 (ddd, J = 14.6, 10.9, 4.5, 2H), 2.17 (dm, J = 14.7, 2H), 3.48 (s, 2H), 3.53 (dt, J = 11.9, 4.5 Hz, 2H), 3.84 (dt, J = 11.9, 4.5 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H); ^{13}CNMR ($CDCl_3$)δ 14.27 (q), 33.17 (t), 40.16 (t), 46.05 (s), 61.29 (t), 64.97 (t), 172.91 (s); CIMS (M^+ + H): 251, (M^+ + NH_4+) 268.

4-(chloromethyl)tetrahydropyran-4-carboxylic acid ethyl ester: IR (neat) 1734 cm^{-1}; ^{1}HNMR ($CDCl_3$) 1.30 (q, J = 7.1 Hz, 3H), 1.59 (ddd, J = 14.6, 10.9, 4.5, 2H), 2.16 (dm, J = 14.7, 2H), 3.53 (dt, J = 11.9, 4.5 Hz, 2H), 3.61 (s, 2H), 3.84 (dt, J = 11.7, 4.3 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 14.24 (q), 32.14 (t), 46.69 (s), 51.40 (t), 61.29 (t), 64.85 (t), 173.01 (s); CIMS (M^+ + H): 207. Anal. Calcd. for $C_9H_{15}ClO_3$: C, 52.31; H, 7.32. Found: C, 52.51; H, 7.30.

6C. Alternative Preparation of a Compound of Formula (13) where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran, and X is *p*-Tosyl

To a solution of tetrahydropyran-4-carboxylic acid ethyl ester (820 mg, 4.356 mmol) in pyridine (10 ml) at 0°C, was added *p*-toluenesulfonyl chloride (997 mg, 5.23 mmol), and the mixture allowed to warm to room temperature over 1 hour period. The mixture was stirred 36 hours and partitioned between methylene chloride (150 ml) and 3N aqueous hydrochloric acid (50 ml). The organic layer was washed with 25 ml of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), concentrated and the residue chromatographed over 45 g of silica gel, eluting with 30% ethyl acetate/hexanes, to afford the tosylate as a white solid (1.03 g, 69%). mp 87.7-88.6 °C; IR (KBr) 1717 cm^{-1}; 1 NMR ($CDCl_3$) δ 1.21 (q, J = 17.1 Hz, 3H), 1.52 (ddd, J = 13.4, 10.6, 4.1 Hz, 2H), 2.00 (dm, J = 13.4 Hz, 2H), 2.46 (s, 3H), 3.49 (ddd, J = 11.7, 10.6, 2.5 Hz, 2H), 3.76 (dt, J = 11.9, 4.1 Hz, 2H), 4.03 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 7.35; ^{13}C NMR ($CDCl_3$) δ 14.10 (q), 21.67 (q), 30.43 (t), 44.93 (s), 61.37 (t), 64.43 (t), 74.65 (t), 127.95 (d), 129.89 (d), 132.67 (s), 145.05 (s), 172.57 (s); HRMS Calcd for $C_{16}H_{22}O_6$: 343.1215. Found: 343.1217. Anal. Calcd. for $C_{16}H_{22}O_6$: C, 56.12; H, 6.48. Found: C, 56.22; H, 6.46.

EXAMPLE 7

Preparation of Compounds of Formula Ia

7A. Preparation of Ia where R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached represent Piperidine, and R^5 is Diphenylether, from a Compound of Formula (4)

1. 4-Phenoxythiophenol (7.4 g, 36.3 mmol), 4-carboxymethylene-*N*-CBZ-piperidine (10 g, 36.3 mmol) and piperidine (1.8 ml, 36.3 mmol) were stirred overnight at 100-110°C in a sealed flask. After cooling, the crude reaction mixture was partitioned between ethyl acetate and 1N hydrochloric acid, the organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a yellow solid. The solid was triturated in 1:1 (v/v) ethyl ether/hexane (500 ml) to give 2-[4-(4-phenoxyphenylthio)-*N*-CBZ-piperidin-4-yl]-acetic acid as a white solid.

2. A solution of 2-[4-(4-phenoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetic acid (150 mg, 0.29 mmole) in dry 1,2 dichloroethane (3 ml) under nitrogen was cooled to -10°C and saturated with hydrochloric acid gas for 15 minutes. The reaction vessel was then sealed and the solution stirred for two days at 25°C. The tube was cooled to -10°C prior to opening to release gaseous hydrochloric acid, and then allowed to warm to 25°C. The solvent was removed *in vacuo* and the product triturated with ethyl acetate to give 2-[4-(4-phenoxyphenylthio)-piperidin-4-yl)]-acetic acid hydrochloride as a white powder. ^{1}HNMR (CD_3OD): 7.93 (d,2H); 7.45 (t,2H); 7.27 (t,1H), 7.14 (t,4H); 3.52 (m,2H); 3.25 (m,2H); 2.70 (s,2H), 2.35 (m,4H).

7B. Preparation of Ia where R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached represent Cyclopentyl, and R^5 is Diphenylether, from a Compound of Formula (4)

A mixture of cyclopentylideneacetic acid (2 mmol) and *p*-(phenoxy)-thiophenol (2 mmol) was heated at 110°C under nitrogen in the presence of piperidine (100 µL) for 24 hours. The residue was dissolved in ethyl acetate and washed with dilute hydrochloric acid. The organic layer was separated, dried and evaporated under reduced pressure to give crude 2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetic acid, which can be used in the next reaction without further purification.

7C. Preparation of Ia where R^1, R^2 and R^3 are Hydrogen, R^4 is Benzyl, and R^5 is 4-Bromophenyl

A mixture of *E*-2-benzylacrylic acid (1 g) and *p*-bromothiophenol (1.12 g) were stirred overnight at 110°C in the presence of piperidine (300 µL). The residue was partitioned between ethyl acetate and dilute hydrochloric acid. The organic layer was separated, dried and evaporated under reduced pressure to give 3-benzyl-3-(4-bromophenylthio)-propionic acid (Iaa), which was used in the next reaction with no further purification.

7D. Preparation of Ia where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl, from a Compound of Formula (10)

2,7-dioxa-spiro[3.5]nonane-1-one (10.8 g), obtained as described in Example 5H, was immediately dissolved in *N,N*-dimethylformamide (95 ml) and slowly added to a solution containing the sodium salt of 4-(4-chlorophenoxy)thiophenol (generated by the addition of sodium hydride powder (2.14 g, 89.2 mmol) to a solution of 4-(4-chlorophenoxy)thiophenol (15.83 g, 66.8 mmol) in *N,N*-dimethylformamide (19 ml) at 0°C and stirring for 30 minutes) over a 10-15 minute period, and then stirred an additional 15 minutes. The resulting slurry was heated to 40°C, stirred for 5 minutes, *tert*-butanol (2 ml) was added, and the mixture cooled to room temperature over 20 minutes. The majority of the *N,N*-dimethylformamide was removed *in vacuo*, the pH adjusted to 9.2, the resultant slurry diluted with 30% diethyl ether-hexanes (120 ml) and filtered. The filter cake was washed with additional portions of ether (3 x 70 ml), acidified to pH 3.5 with 2N aqueous hydrochloric acid, and extracted into methylene chloride (4 x 350 ml). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*. The solid residue was recrystallized from the minimum amount of methylene chloridehexanes to afford pure 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid as a white crystalline solid (19.50 g). mp 140.6-141.9°C; IR (KBr) 3429 (br), 1732 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.54 (ddd, *J* = 14.2, 10.0, 4.2 Hz, 2H), 1.95 (dm, *J* = 14.2 Hz, 2H), 3.19 (s, 2H), 3.56 (ddd, *J* = 11.8, 10.0, 4.2 Hz, 2H), 3.70 (dt, J = 11.8, 4.2 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 4H), 12.66 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 33.06 (t), 43.56 (t), 45.03 (s), 64.13 (t), 119.43 (d), 120.11 (d), 110.43 (d), 127.35 (s), 129.80 (d), 131.09 (s), 131.59 (d), 154.90 (s), 155.50 (s), 175.25 (s); HRMS Cald. for $C_{19}H_{19}SO_4Cl$: 378.0693. Found: 378.0685. Anal. Calcd. for $C_{19}H_{19}SO_4Cl.O.25\ H_2O$: C,59.53; H, 513. Found: C, 59.53; H, 5.07.

Similarly, replacing 4-(4-chlorophenoxy)thiophenol with 4-(4-bromophenoxy)thiophenol and 4-(4-fluorophenoxy)thiophenol, the following compounds were prepared:

4-[4-(4-bromophenoxy)phenylthiomethyl]tetrahydropyran-4-carboxylic acid: mp 143.7-144.5 °C; IR (KBr) 3434 (br), 1732 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.54 (ddd, *J* = 13.8, 10.1, 4.3 Hz, 2H), 1.94 (dm, *J* = 13.5 Hz, 2H), 3.19 (s, 2H), 3.37 (ddd, *J* = 11.8, 10.1, 2.5 Hz, 2H), 3.70 (dt, *J* = 11.8 Hz, 4.0 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 12.68 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 33.04 (t),43.34 (t), 45.00 (s), 64.10 (t), 115.14 (s), 119.59 (d), 120.53 (d), 131.15 (s), 131.51 (d), 132.77 (s), 154.71 (s), 156.06 (s), 175.28 (s); EIMS (M^+): 424. Anal. Calcd. for $C_{19}H_{19}SO_4Br$: C, 53.91; H, 4.52. Found: C, 53.53; H, 4.54;

4-[4-(4-fluorophenoxy)phenylthiomethyl]tetrahydropyran-4-carboxylic acid: mp 143.0-143.4 °C; IR (KBr) 3436 (br), 1721 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.54 (ddd, *J* = 13.5, 10.1, 4.0 Hz, 2H), 1.94 (dm, *J* = 13.5 Hz, 2H), 3.17 (s, 2H), 3.38 (td, *J* = 11.8, 2.5 Hz, 2H), 3.70 (dt, *J* = 11.8 Hz, 4.0 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H),7.05 (dd, *J* = 9.2. 4.6 Hz, 2H), 7.21 (dd, *J* = 9.1, 8.4 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 12.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.05 (t), 43.65 (t),

45.49 (s), 64.12 (t), 116.53 (dd, J_{C-F} = 23.2 Hz), 118.71 (d), 120.63 (dd, J_{C-F} = 8.5 Hz), 130.31 (s), 131.69 (d), 152.38 (s), 155.85 (s), 158.29 (d, J_{C-F} = 239.9 Hz), 175.28 (s); EIMS (M^+): 362. Anal. Calcd. for $C_{19}H_{19}SO_4F$: C, 62.97; H, 5.28. Found: C, 62.79; H, 5.26.

7E. Alternative Preparation of Ia where R^1 and R^2 are both Methyl. R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl

Sodium hydride powder (0.86 g, 35.8 mmol) was added to a mixture of 4-(4-chlorophenoxy)thiophenol (3.55 g, 15 mmol) in *N,N*-dimethylformamide (12 ml) at 0°C. The mixture was warmed to room temperature over 5 minutes, stirred for an additional 20 minutes, and solid chloropivalic acid (1.64 g, 12.0 mmol) was added in one portion. This mixture was heated to 80°C for 18 hours, cooled to room temperature, and water (1 ml) added. The residue was partitioned between methylene chloride (50 ml) and 2N hydrochloric acid (25 ml). The aqueous layer was separated and washed with additional methylene chloride (2 x 25 ml). The combined organic extracts were dried over magnesium sulfate, concentrated *in vacuo*. Chromatography over silica gel, and eluting with 5% methanol/methylene chloride, gave slightly impure 3-[4-(4-chlorophenoxy)-phenylthio]-2,2-dimethyl propionic acid (4 g, 99%). This material was recrystallized from the minimum amount of diethyl ether/hexanes to afford analytically pure acid as a white solid (3.20 g, 80%). mp 84.4-84.9°C; IR (KBr) 3433 (br), 1732 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.19 (s, 6H), 3.14 (s, 2H), 6.97 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.9, 2H), 7.40 (d, J = 8.8 Hz, 2H), 12.36 (br s, 1H). EIMS(M+): 378. Anal. Calcd. for $C_{17}H_{17}SO_3Cl$: C, 60.62; H, 5.09. Found: C, 60.31; H, 4.96.

7F. Preparation of Ia where R^1 and R^2 when taken together with the Carbon to which they are attached represent *N*-BOC-Piperidine. R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl, from a Compound of Formula (10b)

7-(*tert*-Butoxycarbonyl)-2-oxa-7-azaspiro[3.5]nonan-1-one obtained in Example 5I above, was immediately dissolved in *N,N*-dimethylformamide (4 ml), slowly added to a solution containing the sodium salt of 4-(4-chlorophenoxy)thiophenol (generated by the addition of sodium hydride power (340 mg, 14.17 mmol) to a solution of 4-(4-chlorophenoxy)thiophenol (3.00 g, 12.7 mmol) in *N,N*-dimethylformamide (19 ml), at 0°C and stirred for 30 minutes) over a 10-15 minute period, and was stirred an additional 15 minutes. The resulting slurry was heated to 80°C, stirred for 5 minutes, *tert*-butanol (2 ml) added, and the mixture cooled to room temperature over 20 minutes. The majority of the *N,N*-dimethylformamide was removed *in vacuo*, the pH adjusted to 3.5 using 2M aqueous hydrochloric acid and extracted into ethyl acetate (4 x 150 ml). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo* and the residue chromatographed over silica gel, eluting with 1% to 10% methanol/methylene chloride, to afford the piperidine acid, 4-[4-(4-chlorophenoxy)phenylthiomethyl]-*N*-(*tert*-butoxycarbonyl)-piperidin-4-yl carboxylic acid as a pale yellow oil (5 g, 89%). ^{1}HNMR (OH not observed; $CDCl_3$) δ 1.37 (s, 9H), 1.55 (m_c, 2H), 2.10 (m_c, 2H), 3.05 (m_c, 2H), 3.06 (s, 2H), 3.72 (m_c, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 7.21 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 8.7 Hz, 4H).

7G. Preparation of Ia where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, R^5 is 4-(4-Chlorophenoxy)phenyl, from a Compound of Formula Ia where R is Ethyl

To a solution of 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid ethyl ester (70 mg, 0.17 mmol) in ethanol (2 ml) containing two drops of water, was added potassium hydroxide (58.3 mg, 1.04 mmol). The mixture was refluxed for 13 hours, cooled to room temperature, acidified to pH 4, and extracted with ethyl acetate (4 x 50 ml). The combined organic layers were dried over magnesium sulfate, and concentrated to afford 4-[4-(4-chlorophenoxy)-phenylthiomethyl]-tetrahydropyran-4-carboxylic acid (66 mg, 100%), which is spectroscopically identical to that isolated from the prior procedure of Example 7D.

7H. Preparation of Ia where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, R^5 is 4-(4-Bromophenoxy)phenyl, from a Compound of Formula Ia where R is Ethyl

Similarly, following the procedure of Example 7G above, 4-[4-(4-bromophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid and 4-[4-(4-fluorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid were prepared.

7I. Preparation of Ia where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, R^5 is 4-(4-Chlorophenoxy)phenyl, and R is Methyl, from the Corresponding Carboxylic Acid

To a solution of 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid (580 mg, 1.53 mmol) and *N, N*-dimethylformamide catalyst (22 μL) in methylene chloride (15 ml) at 0°C was added oxalyl chloride (0.33 ml, 3.83 mmol) dropwise over 10 minutes. The mixture was warmed to room temperature over 1 hour, the partial slurry stirred an additional 12 hours, and concentrated *in vacuo* until the theoretical mass of the acid chloride was obtained. The residue was suspended in tetrahydrofuran (7.5 ml), and methanol (0.19 ml, 4.59 mmol), followed by triethylamine (0.64 ml, 4.59 mmol) was added. The mixture was heated to reflux for 14 hours, concentrated, and the resulting residue partitioned between methylene chloride (150 ml) and 1M aqueous hydrochloric acid (50 ml). The aqueous layer was back extracted with additional portions of methylene chloride (2 x 30 ml), the combined extracts dried over magnesium sulfate, and concentrated to afford crude 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid methyl ester, which was taken directly into the next reaction without further purification. ^{1}HNMR ($CDCl_3$) δ 1.62 (m_c, 2H), 2.15 (dm, *J* = 13.6 Hz, 2H), 3.13 (s, 2H), 3.47 (td, *J* = 11.9, 2.4 Hz, 2H), 3.59 (s, 3H), 3.81 (dt, *J* = 12.0, 4.1 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H).

7J. Preparation of Ia where R^1 and R^2 taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, R^5 is 4-4-Chlorophenoxy)phenyl, and R is Ethyl, from a Compound of Formula (13)

4-(Iodomethyl)tetrahydropyran-4-carboxylic acid ethyl ester (300 mg, 1 mmol) was added to a solution containing the sodium salt of 4-(4-chlorophenoxy)thiophenol (generated by the addition of sodium hydride powder (36 mg, 1.5 mmol) to a solution of 4-(4-chlorophenoxy)thiophenol (262 mg, 1.1 mmol) in *N,N*-dimethylformamide (2 ml) at 0°C and stirring for 30 minutes). The mixture was warmed to room temperature over 5 minutes, stirred for an additional 20 minutes, cooled to room temperature, and 1M aqueous hydrochloric acid (5 ml) added. The mixture was then partitioned between ethyl acetate (100 ml) and 2M hydrochloric acid (25 ml). The aqueous layer was separated and washed with additional ethyl acetate (2 x 50 ml). The organic extracts were combined, washed with 1M sodium hydroxide (2 x 30 ml), dried over magnesium sulfate, concentrated *in vacuo*. Chromatography over silica gel, and eluting with 20% ethylacetate/ hexanes, yielded pure 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid ethyl ester (370 mg, 91%), followed by impure 4-[4-(4-chlorophenoxy)-phenylthiomethyl]tetrahydropyran-4-carboxylic acid ethyl ester (40 mg). IR (KBr) 1728 cm^{-1}; ^{1}HNMR ($CDCl_3$) 1.23 (q, *J* = 7.1 Hz, 3H), 1.56 (ddd, *J* = 14.6, 10.9, 4.4, 2H), 1.63 (ddd, *J* = 14.6, 5.7, 3.3, 2H), 3.13 (s, 2H), 3.51 (ddd, *J* = 11.8, 11.1, 2.4 Hz, 2H), 3.80 (dt, *J* = 11.8, 4.1 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.20 (q), 33.72 (t), 45.72 (t), 46.07 (s), 60.92 (t), 65.06 (t), 119.29 (d), 120.20 (d), 128.43 (s), 129.85 (d), 130.57 (s), 133.05 (s), 155.40 (s), 156.21(s), 174.02 (s); EIHRMS Calcd. for $C_{21}H_{23}SO_4Cl$ (M^+): 406.1006. Found: 406.1008. Anal. Calcd. for $C_{21}H_{23}SO_4Cl$: C, 61.98; H, 5.70. Found: C, 61.86; H, 5.68.

7K. Preparation of Ia where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, R^5 is 4-(4-Bromophenoxy)phenyl, and R is Ethyl, from a Compound of Formula (13)

Similarly, replacing 4-(4-chlorophenoxy)thiophenol with 4-(4-bromophenoxy)thiophenol, and following the procedures of Example 7J above, 4-[4-(4-bromophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid ethyl ester was prepared (2.10 g, 93%). IR (KBr) 1728 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.22 (q, *J* = 7.1 Hz, 3H), 1.60 (ddd, *J* = 14.6, 10.9, 4.5, 2H), 2.14 (ddd, *J* = 14.6, 5.7, 3.3, 2H), 3.13 (s, 2H), 3.81 (ddd, *J* = 11.8, 11.1, 2.4 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 9.0 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 14.20 (q), 33.71 (t), 45.69 (t), 46.05 (s), 60.92 (t), 65.05 (t), 116.06 (s), 119.40 (d), 120.59 (d), 130.69 (s), 132.81 (d), 133.03 (s), 156.04 (s), 156.16 (s), 174.01 (s); EIHRMS Calcd. for $C_{21}H_{23}SO_4Br$ (M^+): 450.0500. Found: 450.0505. Anal. Calcd. for $C_{21}H_{23}SO_4Cl$: C, 55.88; H, 5.14. Found: C, 55.52; H, 5.09.

Similar reactions were carried out, starting from compounds of Formula (13) where X is iodo, bromo, and chloro, and moderate to good yields were obtained in all cases.

7L. Preparation of Ia, varying R^1, R^2, R^3, R^4, and R^5

Similarly, optionally replacing 4-carboxymethylene-*N*-CBZ-piperidine with other *N*-protected compounds of Formula (4) and following the procedures of Example 7A (1) and (2) above, or optionally replacing cyclopentylideneacetic acid with other compounds of Formula (4) and following the procedures of Example 7B above, and optionally replacing p-phenoxythiophenol with other compounds of Formula (5), the following compounds of Formula Ia were prepared:

2-[4-(4-methoxyphenylthio)-*N*-CBZ-piperidin-4-yl-]-acetic acid;
2-[4-(4-methoxyphenylthio)-piperidin-4-yl)]-acetic acid;
2-benzyl-3-(3-methoxyphenylthio)-propionic acid;
2-benzyl-3-(4-methoxyphenylthio)-propionic acid;
3-benzyl-3-(4-methoxyphenylthio)-propionic acid;
3,3-dimethyl-3-[(4-chlorophenoxy)phenylthio]-propionic acid;
2-{4-[4-(4-fluorophenoxy)phenylthio]-piperidin-4-yl}-acetic acid;
2-{4-[4-(4-fluorophenoxy)phenylthio}-*N*-CBZ-piperidin-4-yl}-acetic acid;
3-benzyl-3-[(4-phenylthiophenyl)thio]-propionic acid;
3-benzyl-3-(phenylthio)-propionic acid;
3-benzyl-3-(4-phenoxphenylthio)-propionic acid;
3-benzyl-3-[(4-biphenyl)thio]-propionic acid;
3-benzyl-3-(2-naphthylthio)-propionic acid;
3-benzyl-3-(4-methoxystyrylphenylthio)-propionic acid;
3-cyclopentylmethyl-3-(4-methoxyphenylthio)-propionic acid;
3-cyclopentylmethyl-2-isopropyl-3-(4-methoxyphenylthio)-propionic acid;
3-ethyl-2-methyl-3-(4-methoxyphenylthio)-propionic acid;
3,3-dimethyl-(4-methoxyphenylthio)-propionic acid;
2-[1-(4-methoxyphenylthio)-cyclopent-1-yl]-acetic acid;
2-[4-(4-methoxyphenylthio)-cyclohexanone-4-yl]-acetic acid ethylene ketal;
2-[1-(4-methoxyphenylthio)-(4-methylcyclohex-1-yl]-acetic acid;
2-[1-(4-phenoxyphenylthio)-cyclohex-1-yl]-acetic acid;
2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetic acid;
{4-[4-(4-benzo[b]thiophen-2-yl-phenoxy)phenylthio)-tetrahydropyran-4-yl]-acetic acid;
2-{4-[4-(phenylmethyl)phenylthio]-tetrahydropyran-4-yl}-acetic acid;
2-{4-[4-(4-fluorophenoxy)phenylthio]-tetrahydropyran-4-yl}-acetic acid;
2-{4-[4-(4-chlorophenoxy)phenylthio]-tetrahydropyran-4-yl}-acetic acid: mp 138.5-138.8 °C; ^{1}HNMR ($CDCl_3$, OH not seen) δ 1.73 (d, J = 14.7, 2H), 1.91 (ddd, J = 14.7, 10.1, 4.3 Hz, 2H), 2.58 (s, 2H), 3.76 (dt, J = 11.8, 4.1 Hz, 2H), 4.02 (dt, J = 11.8, 2.6 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 7.33 (d, J = 8.9 Hz, 2H), 7.53 (d, J = 8.8 Hz, 4H); FABMS (M^+): 379.2. Anal. Calcd. for $C_{19}H_{19}SO_4Cl$: C, 60.23; H, 5.05. Found: C, 60.39; H, 5.01;
2-{4-[4-(4-chlorophenoxy)phenylthio]-tetrahydropyran-4-yl}-acetic acid;
2-{4-[4-(4-bromophenoxy)phenylthio]-tetrahydropyran-4-yl}-acetic acid;
2-[4-(4-phenoxyphenylthio)-tetrahydrothiopyran-1,1-dioxide-4-yl]-acetic acid;
trans-2-(4-methoxyphenylthio)-cyclopentanecarboxylic acid; and
2-(4-methoxyphenylthio)-cyclohexanecarboxylic acid.

7M. Preparation of Ia, varying R^1, R^2, R^3, R^4, and R^5

Similarly, optionally replacing 2,7-dioxa-spiro[3.5]nonane-1-one with other compounds of Formula (10) and following the procedures of Example 7D above, and optionally replacing 4-(4-chlorophenoxy)-thiophenol with other compounds of Formula (5), the following compounds of Formula Ia were prepared:

4-[4-(4-fluorophenoxy)phenylthiomethyl]tetrahydropyran-4-carboxylic acid;
4-[4-(4-bromophenoxy)phenylthiomethyl]tetrahydropyran-4-carboxylic acid;
3-(4-benzoylphenylthio)-2,2-dimethyl propionic acid;
3-[4-(4-chlorophenoxy)phenylthio]-2,2-dimethyl propionic acid;
4-[(4-phenoxypyrid-4-yl)thiomethyl]tetrahydropyran-4-carboxylic acid: ^{1}HNMR (OH not observed; $CDCl_3$) δ 1.65 (m_c, 2H), 2.16 (dm, J = 14.2 Hz, 2H), 3.20 (s, 2H), 3.57 (tm, J = 11.4 Hz, 2H), 3.84 (dm, J = 12.0 Hz, 2H), 6.87 (d, J =6.2 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.9 Hz, 2H), 8.43 (d, J = 6.0 Hz, 2H).

7N. Preparation of Ia, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 7 above, other compounds of Formula Ia are prepared.

EXAMPLE 8

Preparation of Compounds of Formula Iba

8A. Preparation of Iba where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl

Oxalyl chloride (37.5 ml, 429.5 mmol) was added dropwise over 10 minutes to a suspension of 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid (65.1 g, 171.8 mmol) and *N,N*-dimethylformamide catalyst (2 ml) in methylene chloride (1 litre) at 0°C. The mixture was warmed to room temperature over 1 hour and the resultant partial slurry stirred an additional 20 hours, concentrated under reduced pressure until the theoretical mass of the acid chloride was obtained. This mixture was dissolved in methylene chloride (600 ml), cooled to 0°C, and *N,O*-bis(trimethylsilyl)hydroxylamine (109.1 ml, 510.45 mmol) added dropwise over 10 minutes. The mixture was immediately warmed to room temperature, stirred 3 hours, and recooled to 0°C. Aqueous 2.4M hydrochloric acid solution (400 ml, 960 mmol) was added to the solution, causing precipitation of the hydroxamic acid product within several minutes after the addition. The slurry was stirred an additional 30 minutes and filtered. The filter cake was washed with water (3 x 30 ml) and 50% diethyl ether-hexanes (2 x 25 ml) and dried at 70°C to afford 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) (61.8 g, 92%). mp 146.6-148.0 °C; IR (KBr) 3426 (br), 1636 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.54 (ddd, *J* = 13.8, 10.2, 4.0 Hz, 2H), 2.00 (dm, *J* = 13.8 Hz, 2H), 3.16 (s, 2H), 3.39 (m, 2H), 3.66 (dt,*J*= 11.7,3.8 Hz, 2H), 6.98 (d,*J* = 8.8Hz, 2H), 7.02 (d,*J*=9.0Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 2H), 8.78 (s, 1H), 10.63 (s, 1H); ^{13}CNMR ($CDCl_3$) δ 32.79 (t), 43.60 (s), 43.70 (t), 63.93 (t), 119.56 (d), 120.07 (d), 127.19 (s), 129.85 (d), 131.24 (d), 131.34 (s), 154.62 (s), 155.59 (s), 169.69 (s); FABHRMS Calcd. for $C_{19}H_{21}NSO_4Cl$ (M^+ + H): 394.0880. Found: 378.0872. Anal. Calcd. for $C_{19}H_{20}NSO_4Cl$: C, 57.94; H, 5.12; N, 3.56. Found: C, 57.98; H, 5.04; N, 3.68.

8B. Alternative Preparation of Iba where R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl

Oxalyl chloride (37.5 ml, 429.5 mmol) was added dropwise over 10 minutes to a solution of 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid (65.1 g, 171.8 mmol) and *N,N*-dimethylformamide catalyst (2 ml) in methylene chloride (1 litre) at 0°C. The mixture was warmed to room temperature over 1 hour, and the resultant partial slurry stirred an additional 20 hours and concentrated *in vacuo* until the theoretical mass of the acid chloride was obtained. A solution of the acid chloride mixture (650 mg, 1.68 mmol) in methylene chloride (3.4 ml) was added dropwise over 2 minutes to a solution of 50% aqueous hydroxylamine (556 mg) in 2:1 tetrahydrofuran/*tert*-butanol (5.1 ml). The mixture was stirred 1.5 hours and concentrated until approximately 1 ml of aqueous solution was remaining. The slurry was filtered, washed with 1:1 diethyl ether-hexanes (3 X 15 ml) and the solid dried overnite at 70°C in a vacuum oven, to afford 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) (584 mg, 91%). mp 146.6-148.0 °C; IR (KBr) 3426 (br), 1636 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.54 (ddd, *J* = 13.8, 10.2, 4.0 Hz, 2H), 2.00 (dm, *J* = 13.8 Hz, 2H), 3.16 (s, 2H), 3.39 (m, 2H), 3.66 (dt, *J* = 11.7, 3.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 2H), 8.78 (s, 1H), 10.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.79 (t), 43.60 (s), 43.70 (t), 63.93 (t), 119.56 (d), 120.07 (d), 127.19 (s), 129.85 (d), 131.24 (d), 131.34 (s), 154.62 (s), 155.59 (s), 169.69 (s); FABHRMS Calcd. for $C_{19}H_{21}NSO_4Cl$ (M^+ + H): 394.0880. Found: 378.0872. Anal. Calcd. for $C_{19}H_{20}NSO_4Cl$: C, 57.94; H, 5.12; N, 3.56. Found: C, 57.98; H, 5.04; N, 3.68.

8C. Preparation of Iba, varying R^1, R^2, R^3, R^4, and R^5

Similarly, replacing 4-[4-(4-chlorophenoxy)phenyl-thiomethyl]-tetrahydropyran-4-carboxylic acid with other compounds of Formula Ia and following the procedures of Example 8A above, the following compounds of Formula Iba were prepared:

4-[4-(4-fluorophenoxy)phenylthiomethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 146.2-146.5 °C; IR (KBr) 3431 (br), 1628 cm^{-1}; ^{1}HNMR ($CDCl_3$; NH and OH not observed) δ 1.35 (ddd, *J* = 13.8, 10.2, 4.0 Hz, 2H), 1.83 (dm, *J* = 13.8 Hz, 2H), 2.85 (s, 2H), 3.23 (m, 2H), 3.46 (dt, *J* = 11.9, 3.9 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.65-6.78 (m, 4H),7.06 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.99 (t), 44.27 (s), 45.49 (t), 64.63 (t), 116.28 (dd, J_{C-F} = 23.2 Hz), 118.64 (d), 120.49 (dd, J_{C-F} = 8.5 Hz), 130.41 (s), 132.49 (d), 152.46 (s), 156.49 (s), 160.29 (d, J_{C-F} = 241.9 Hz), 170.23 (s); FABMS (M^+ + H): 378. Anal. Calcd. for $C_{19}H_{20}NSO_4F$: C, 60.46; H, 5.34; N, 3.71. Found: C, 60.08; H, 5.29; N, 3.65.

4-[4-(4-bromophenoxy)phenylthiomethyl]tetrahydropyran-4-*N*-hydroxycarboxamide: mp 153.1-154.0 °C; IR (KBr) 3434 (br), 1634 cm^{-1}; 1HNMR ($CDCl_3$; NH and OH not observed) δ 1.68 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 2H), 2.13 (dm, *J* = 14.0 Hz, 2H), 3.15 (s, 2H), 3.55 (ddd, *J* = 12.0, 10.2, 2.5 Hz, 2H), 3.76 (dt, *J* = 12.0 Hz, 4.1 Hz, 2H), 6.87

(d, J = 9.0 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 33.01 (t), 44.32 (s), 45.40 (t), 64.65 (t), 115.95 (s), 119.50 (d), 120.53 (d), 130.67 (s), 132.76 (d), 132.80 (d), 155.92 (s), 156.16 (s), 170.60 (s); FABMS (M^+ + H): 438. Anal. Calcd. for $C_{19}H_{20}NSO_4Br$: C, 52.06; H, 4.60; N, 3.20. Found: C, 51.84; H, 4.52; N, 3.54.

3-(4-benzoylphenylthio)-2,2-dimethyl-N-hydroxypropionamide;
3-[4-(4-chlorophenoxy)phenylthio]-2,2-dimethyl-N-hydroxypropionamide: mp 114.7-115.3 °C; ^{1}HNMR ($CDCl_3$) δ 1.30 (s, 6H), 3.14 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H); FABHRMS Calcd. for $C_{17}H_{18}NSO_3Cl$ (M^+ + H): 352.0772. Found: 352.0774. Anal. Calcd. for $C_{17}H_{18}NSO_3Cl$: C, 58.03; H, 5.16; N, 3.98. Found: C, 57.85; H, 5.10; N, 4.12.
3,3-dimethyl-3-[(4-chlorophenoxy)phenylthio]-N-hydroxypropionamide;
{4-[4-(4-benzo[b]thiophen-2-yl-phenoxy)phenylthio)-tetrahydropyran-4-yl]-N-hydroxyacetamide;
2-{4-[4-(phenylmethyl)phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-chlorophenoxy)phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide; and
2-{4-[4-(4-bromophenoxy)phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide.

8D. Preparation of Iba, varying R^1, R^2, R^3, R^4, and R^5

Similarly, replacing 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid with other compounds of Formula Ia and following the procedures of Example 8A above, other compounds of Formula Iba are prepared, for example:

4-(4-phenoxyphenylthiomethyl)tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-fluorophenoxy)phenylthiomethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylthiomethyl]piperidine-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylthiomethyl]-1-methylpiperidine-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylthiomethyl]-1-(cyclopropyl-methyl)piperidine-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylthiomethyl]-1-acetylpiperidine-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylthiomethyl]-1-(3-pyridyl)-piperidine-4-(*N*-hydroxycarboxamide);
4-[4-(4-chlorophenoxy)phenylthiomethyl]-1-(3-pyridoyl)-piperidine-4-(*N*-hydroxycarboxamide);
2-[4-(4-methoxyphenylthio)-*N*-CBZ-piperidin-4-yl-]-*N*-hydroxyacetamide;
2-[4-(4-methoxyphenylthio)-piperidin-4-yl)]-*N*-hydroxyacetamide;
2-benzyl-3-(3-methoxyphenylthio)-*N*-hydroxypropionamide;
2-benzyl-3-(4-methoxyphenylthio)-*N*-hydroxypropionamide;
3-benzyl-3-(4-methoxyphenylthio)-*N*-hydroxypropionamide;
2-{4-[4-(4-fluorophenoxy)phenylthio]-piperidin-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)phenylthio]-*N*-CBZ-piperidin-4-yl}-*N*-hydroxyacetamide;
3-benzyl-3-[(4-phenylthiophenyl)thio]-*N*-hydroxypropionamide;
3-benzyl-3-(phenylthio)-*N*-hydroxypropionamide;
3-benzyl-3-(4-phenoxphenylthio)-*N*-hydroxypropionamide;
3-benzyl-3-[(4-biphenyl)thio]-*N*-hydroxypropionamide;
3-benzyl-3-(2-naphthylthio)-*N*-hydroxypropionamide;
3-benzyl-3-(4-methoxystyrylphenylthio)-*N*-hydroxypropionamide;
3-cyclopentylmethyl-3-(4-methoxyphenylthio)-*N*-hydroxypropionamide;
3-cyclopentylmethyl-2-isopropyl-3-(4-methoxyphenylthio)-*N*-hydroxypropionamide;
3-ethyl-2-methyl-3-(4-methoxyphenylthio)-*N*-hydroxypropionamide;
3,3-dimethyl-(4-methoxyphenylthio)-*N*-hydroxypropionamide;
2-[1-(4-methoxyphenylthio)-cyclopent-1-yl]-*N*-hydroxyacetamide;
2-[4-(4-methoxyphenylthio)-cyclohexanone-4-yl]-*N*-hydroxyacetamide ethylene ketal;
2-[1-(4-methoxyphenylthio)-(4-methylcyclohex-1-yl]-*N*-hydroxyacetamide;
2-[1-(4-phenoxyphenylthio)-cyclohex-1-yl]-*N*-hydroxyacetamide;
2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
2-[4-(4-phenoxyphenylthio)-tetrahydrothiopyran-1,1-dioxide-4-yl]-*N*-hydroxyacetamide;
trans-2-(4-methoxyphenylthio)-cyclopentanecarboxylic acid; and
2-(4-methoxyphenylthio)-cyclohexanecarboxylic acid.

EXAMPLE 9

Preparation of Compounds of Formula Ib

9A. Preparation of Ib where R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Cyclopentyl, and R^5 is 4-Phenoxyphenyl

The 2-[1-(4-phenoxypheny]thio)-cyclopent-1-yl]-acetic acid obtained in Example 5 was dissolved in methylene chloride (8 ml) and treated with 4-dimethylaminopyridine (180 mg), *O*-(*tert*-butyl)-hydroxylamine hydrochloride (360 mg), triethylamine (540 μL), pyridine (400 μL), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (750 mg). After stirring overnight the reaction mixture was partitioned between ethyl acetate and water, the organic layer separated, and the solvent removed under reduced pressure. Preparative TLC of the residue and elution with 2:1 hexane/ethyl acetate gave *N*-(*tert*-butoxy)-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide (270 mg) as a white foam, which can be used in the next reaction without further purification.

9B. Preparation of Ib where R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Tetrahydropyran, and R^5 is 4-Phenoxyphenyl

O-(*tert*-Butyl)hydroxylamine hydrochloride (9.57 g), 4-methylmorpholine (15.64 ml), hydroxybenzotriazole (6.87 g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (19.5 g) was added to a solution of 2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetic acid (17.5 g) in methylene chloride (200 ml). After stirring for 3 hours at room temperature, 0.5 M hydrochloric acid (200 ml) was added to the mixture, and the mixture extracted with methylene chloride. The solvent was removed from the combined extracts under reduced pressure. Silica gel chromatography of the residue and elution with 35%-80% ethyl acetate/hexane gave *N*-*tert*-butoxy-2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetamide (15.3 g) as an oil, which can be used in the next reaction without further purification.

9C. Preparation of Ib where R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached are *N*-BOC-Piperidine, and R^5 is 4-(4-Chlorophenoxy)phenyl

4-Methylmorpholine (2.60 ml, 23.68 mmol) was added dropwise to a solution of 2-{4-[4-(4-chlorophenoxy)phenylthiomethyl]-*N*-BOC-piperidin-4-yl}-carboxylic acid obtained in Example 6 (2.83 g, 5.92 mmol), *O*-(*tert*-butyl)hydroxylamine hydrochloride (2.23 g, 17.76 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.27 g, 11.84 mmol) in anhydrous methylene chloride (25 ml) cooled to 0°C. After the resulting mixture was allowed to warm to room temperature over 1 hour and stirred for an additional 12 hours, the mixture was partitioned between diethyl ether/1 N aqueous hydrochloric acid (300 ml). The acid layer was back extracted using diethyl ether (2 x 100 ml), and the combined ether extracts dried over magnesium sulfate and concentrated. Chromatography over silica gel, and eluting with 25% ethyl acetate/hexanes, gave *N*-(*tert*-butoxy)-2-{4-[4-(4-chlorophenoxy)phenylthiomethyl]-*N*-BOC-piperidin-4-yl}-carboxamide (2.88 g, 89%). ^{1}HNMR ($CDCl_3$) δ 1.31 (s, 9H), 1.45 (s, 9H), 1.58 (m_c, 2H), 2.10 (br d, *J* = 14.2 Hz, 2H), 3.13 (s, 2H), 3.19 (m_c, 2H), 3.73 (m_c, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 8.15 (br s, 1H).

9D. Preparation of Ib, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 9A above, but replacing 2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetic acid with other compounds of Formula Ia, the following compounds of Formula Ib were prepared:

N-*tert*-butoxy-2-[4-(4-phenoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-*tert*-butoxy-2-[4-(4-methoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-*tert*-butoxy-2-{4-[4-(4-fluorophenoxy)phenylthio]-*N*-CBZ-piperidin-4-yl}-acetamide;
N-*tert*-butoxy-2-{4-[4-(4-fluorophenoxy)phenylthio]-piperidin-4-yl}-acetamide;
N-*tert*-butoxy-2-[4-(4-phenoxyphenylthio)-piperidin-4-yl)]-acetamide;
N-*tert*-butoxy-2-[4-(3-methoxyphenylthio)-piperidin-4-yl)]-acetamide;
N-*tert*-butoxy-2-[4-(4-methoxyphenylthio)-piperidin-4-yl)]-acetamide;
N-*tert*-butoxy-2-benzyl-3-(phenylthio)-propionamide;
N-*tert*-butoxy-3-benzyl-3-(phenylthio)-propionamide;
N-*tert*-butoxy-3-benzyl-3-(4-methoxyphenylthio)-propionamide;
N-*tert*-butoxy-3-benzyl-3-[(4-phenylthiophenyl)thio]-propionamide;
N-*tert*-butoxy-3-benzyl-3-(4-phenoxyphenylthio)-propionamide;
N-*tert*-butoxy-3-benzyl-3-[(4-biphenyl)thio]-propionamide;

N-tert-butoxy-3-benzyl-3-(2-naphthylthio)-propionamide;
N-tert-butoxy-3-benzyl-3-(4-methoxystyrylphenylthio)-propionamide;
N-tert-butoxy-3-cyclopentylmethyl-3-(4-methoxyphenylthio)-propionamide;
N-tert-butoxy-3-cyclopentylmethyl-2-isopropyl-3-(4-methoxyphenylthio)-propionamide;
N-tert-butoxy-3-ethyl-2-methyl-3-(4-methoxyphenylthio)-propionamide;
N-tert-butoxy-3,3-dimethyl-(4-methoxyphenylthio)-propionamide;
N-tert-butoxy-2-[1-(4-methoxyphenylthio)-cyclopent-1-yl]-acetamide;
N-tert-butoxy-2-[1-(4-methoxyphenylthio)-(4-methylcyclohex-1-yl]-acetamide;
N-tert-butoxy-2-[4-(4-phenoxyphenylthio)-cyclohexanone-4-yl]-acetamide ethylene ketal;
N-tert-butoxy-2-[1-(4-phenoxyphenylthio)-cyclohex-1-yl]-acetamide;
N-tert-butoxy-2-[4-(4-methoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-tert-butoxy-2-[4-(4-methoxyphenylthio)-piperidin-4-yl)]-acetamide.
N-tert-butoxy-2-{4-[4-(4-fluorophenoxy)phenylthio]-tetrahydropyran-4-yl}-acetamide;
N-tert-butoxy-2-{4-[4-(4-chlorophenoxy)phenylthio]-tetrahydropyran-4-yl]-acetamide;
N-tert-butoxy-2-[4-(4-phenoxyphenylthio)-tetrahydrothiopyran-1,1-dioxide-4-yl]-acetamide;
N-tert-butoxy-4-[4-(4-pyridyloxy)phenylthiomethyl]-tetrahydropyran-carboxamide: ^{1}HNMR ($CDCl_3$) δ 1.31 (s, 9H), 1.70 (m_c, 2H), 2.14 (dm, J = 11.8 Hz, 2H), 3.21 (s, 2H), 3.63 (m_c, 2H), 3.82 (m_c, 2H), 6.84 (d, J =6.4 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 8.20 (s, 1H), 8.48 (d, J = 5.8 Hz, 2H).
N-tert-butoxy-4-[4-(5-chloro-2-pyridyloxy)phenylthiomethyl]-tetrahydropyran-carboxamide: mp 100.5-102.7 °C; IR (KBr) 3438 (br), 1657 cm^{-1}; ^{1}HNMR (DMSO-d_6) 1.19 (s, 9H), 1.57 (ddd, J = 13.5, 10.1, 4.0 Hz, 2H), 2.05 (dm, J = 13.5 Hz, 2H), 3.34 (s, 2H), 3.42 (m_c, 2H), 3.65 (dm, J = 11.6 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.95 (dd, J = 8.8, 2.7 Hz, 1H), 8.19 (d, J = 2.7 Hz, 1H), 10.37 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 26.66 (q), 33.03 (t), 43.20 (t), 44.25 (s), 64.10 (t), 80.78 (s), 113.00 (d), 121.88 (d), 124.88 (s), 130.43 (d), 132.67 (s), 139.93 (d), 145.51 (d), 151.89 (s), 161.58 (s), 171.64 (s); FABHRMS Calcd. for $C_{22}H_{28}N_2SO_4Cl$ (M^+ + H): 451.1458. Found: 451.1461. Anal. Calcd. for $C_{22}H_{27}N_2SO_4Cl$: C, 58.59; H, 6.03; N, 6.21. Found: C, 58.70; H, 6.05; N, 6.43.
N-tert-butoxy-3-[4-(5-chloro-2-pyridyloxy)phenylthio]-2,2-dimethyl-*N*-hydroxypropionamide: mp 90.8-91.9°C; IR (KBr) 3438 (br), 1651 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.18 (s, 9H), 1.21 (s, 6H), 3.20 (s, 2H), 7.08 (m_c, 3H), 7.40 (d, J = 8.7 Hz, 2H), 7.93 (dd, J = 8.7, 2.7 Hz, 1H), 8.17 (d, J = 2.7 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.67 (q), 26.48 (q), 42.54 (s), 44.31 (t), 80.62 (s), 112.95 (d), 121.79 (d), 125.28 (s), 130.32 (d), 133.31 (s), 139.86 (d), 145.48 (d), 151.77 (s), 161.58 (s), 173.77 (s); FABHRMS Calcd. for $C_{20}H_{26}N_2SO_3Cl$ (M^+ + H): 409.1353. Found: 409.1354. Anal. Calcd. for $C_{20}H_{25}N_2SO_3Cl$: C, 58.74; H, 6.16; N, 6.85. Found: C, 58.91; H, 6.13; N, 7.07.
N-tert-butoxy-2-(4-methoxyphenylmercapto)-cyclohexane-carboxamide; and
N-tert-butoxy-*trans*-2-(4-methoxyphenylmercapto)-cyclopentanecarboxamide.

9E. Preparation of Ib, varying R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 9A above, but replacing 2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetic acid with other compounds of Formula Ia, other compounds of Formula Ib are prepared.

EXAMPLE 10

Preparation of Compounds of Formula Id

10A. Preparation of Id where n is 0, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Cyclopentyl, and R^5 is 4-Phenoxyphenyl

The *N-tert*-butoxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide was dissolved in trifluoroacetic acid (6 ml) and allowed to stand for 24 hours. The acid was evaporated off under reduced pressure and the product purified by preparative TLC, eluting with 6.5% methanol/methylene chloride gave *N*-hydroxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide (100 mg).

10B. Preparation of Id where n is 0, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 10A above, but replacing *N-tert*-butoxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide with other compounds of Formula Ib, the following compounds of Formula Id where n is 0 are prepared:

N-hydroxy-2-[4-(4-phenoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide;

N-hydroxy-2-[4-(4-methoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide;
2-{4-[4-(4-fluorophenoxy)phenylthio]-*N*-CBZ-piperidin-4-yl}-*N*-hydroxy-acetamide;
2-{4-[4-(4-fluorophenoxy)phenylthio]-piperidin-4-yl}-*N*-hydroxy-acetamide;
3-benzyl-*N*-hydroxy-3-(3-methoxyphenylthio)-propionamide;
N-hydroxy-2-[4-(4-phenoxyphenylthio)-piperidin-4-yl)]-acetamide;
N-hydroxy-2-[4-(4-methoxyphenylthio)-piperidin-4-yl)]-acetamide;
2-benzyl-*N*-hydroxy-3-(phenylthio)-propionamide;
3-benzyl-*N*-hydroxy-3-(phenylthio)-propionamide;
3-benzyl-*N*-hydroxy-3-(4-methoxyphenylthio)-propionamide;
3-benzyl-*N*-hydroxy-3-[(4-phenylthiophenyl)thio]-propionamide;
3-benzyl-*N*-hydroxy-3-(4-phenoxyphenylthio)-propionamide;
3-benzyl-*N*-hydroxy-3-[(4-biphenyl)thio]-propionamide;
3-benzyl-*N*-hydroxy-3-(2-naphthylthio)-propionamide;
3-benzyl-*N*-hydroxy-3-(4-methoxystyrylphenylthio)-propionamide;
3-cyclopentylmethyl-*N*-hydroxy-3-(4-methoxyphenylthio)-propionamide;
3-cyclopentylmethyl-*N*-hydroxy-2-isopropyl-3-(4-methoxyphenylthio)-propionamide;
3-ethyl-*N*-hydroxy-2-methyl-3-(4-methoxyphenylthio)-propionamide;
3,3-dimethyl-*N*-hydroxy-(4-methoxyphenylthio)-propionamide;
N-hydroxy-2-[1-(4-methoxyphenylthio)-cyclopent-1-yl]-acetamide;
N-hydroxy-2-[1-(4-methoxyphenylthio)-(4-methylcyclohex-1-yl]-acetamide;
N-hydroxy-2-[1-(4-phenoxyphenylthio)-cyclohex-1-yl]-acetamide;
N-hydroxy-2-[4-(4-methoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-hydroxy-2-[4-(4-methoxyphenylthio)-piperidin-4-yl)]-acetamide;
N-hydroxy-2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetamide; 2-{4-[4-(4-chlorophenoxy)-phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxy-acetamide;
2-{4-[4-(4-fluorophenoxy)phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxy-acetamide, m.p. 50-55°C; and
N-hydroxy-2-[4-(4-phenoxyphenylthio)-tetrahydrothiopyran-1,1-dioxide-4-yl]-acetamide.

10C. Preparation of Id where n is 0, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 10A above, but replacing *N-tert*-butoxy-2-[1-(4-phenoxyphenylthio)cyclopent-1-yl]-acetamide with other compounds of Formula Ib, other compounds of Formula Id where n is 0 are prepared.

EXAMPLE 11

Preparation of Compounds of Formula Id

11A. Preparation of Id where n is 1, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Cyclopentyl, and R^5 is 4-Phenoxyphenyl

A solution of *N*-hydroxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide (45 mg) in acetone (4 ml) was treated with sodium periodate (260 mg) in water (2 ml). Over the course of 24 hours, two additional portions of sodium periodate (260 mg) were added. After complete disappearance of starting material the solution was diluted with methylene chloride, filtered, dried, and the solvent evaporated under reduced pressure. Preparative TLC on silica gel and elution with 10% methanol/methylene chloride gave *N*-hydroxy-2-[1-(4-phenoxyphenylsulfinyl)-cyclopent-1-yl]-acetamide (15 mg), ^{1}H NMR (CDCl3) 7.64 (d,2H), 7.44 (t,2H), 7.30-7.05 (m,5H), 2.97 (d,1H), 2.53 (d,1H), 2.15-1.65 (m,8H).

11B. Preparation of Id where n is 1, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Tetrahydropyran-4-yl, and R^5 is 4-(4-Fluorophenoxy)-phenyl

2-{4-[4-(4-Fluorophenoxy)phenylthio]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide (500 mg) was dissolved in methanol (25 ml). OXONE (400 mg) in water (5 ml) was added. After stirring for 30 minutes, the mixture was partitioned between methylene chloride and water. Preparative TLC on silica gel and elution with 10% methanol/methylene chloride gave 2-{4-[4-(4-fluorophenoxy)phenyl-sulfinyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide (402 mg, m.p. 120°C).

11C. Preparation of Id where n is 1, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 11A or 11B above, but replacing *N*-hydroxy-2-[1-(4-phenoxyphe-

nylthio)-cyclopent-1-yl]-acetamide with other compounds of Formula Id where n is 0, other compounds of Formula Id where n is 1 are prepared, for example;

N-hydroxy-2-[4-(4-phenoxyphenylsulfinyl)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-hydroxy-2-[4-(4-phenoxyphenylsulfinyl)-piperidin-4-yl)]-acetamide;
N-hydroxy-2-[4-(4-methoxyphenylsulfinyl)-*N*-CBZ-piperidin-4-yl)]-acetamide;
2-{4-[4-(4-fluorophenoxy)phenylsulfinyl]-piperidin-4-yl}-*N*-hydroxyacetamide;
N-hydroxy-2-[4-(4-methoxyphenylsulfinyl)-piperidin-4-yl)]-acetamide;
2-benzyl-*N*-hydroxy-3-(4-methoxyphenylsulfinyl)-propionamide;
3-benzyl-*N*-hydroxy-3-(3-methoxyphenylsulfinyl)-propionamide;
3-benzyl-*N*-hydroxy-3-(4-methoxyphenylsulfinyl)-propionamide;
3-benzyl-*N*-hydroxy-3-[(4-phenylthiophenyl)sulfinyl]-propionamide;
3-benzyl-*N*-hydroxy-3-(4-phenoxyphenylsulfinyl)-propionamide;
3-benzyl-*N*-hydroxy-3-[(4-biphenyl)sulfinyl]-propionamide;
3-benzyl-*N*-hydroxy-3-(2-naphthylsulfinyl)-propionamide;
3-benzyl-*N*-hydroxy-3-(4-methoxystyrylphenylsulfinyl)-propionamide;
3-cyclopentylmethyl-*N*-hydroxy-3-(4-methoxyphenylsulfinyl)-propionamide;
3-cyclopentylmethyl-*N*-hydroxy-2-isopropyl-3-(4-methoxyphenylsulfinyl)-propionamide;
3-ethyl-*N*-hydroxy-2-methyl-3-(4-methoxyphenylsulfinyl)-propionamide;
3,3-dimethyl-*N*-hydroxy-(4-methoxyphenylsulfinyl)-propionamide;
N-hydroxy-2[1-(4-methoxyphenylsulfinyl)-cyclopent-1-yl]-acetamide;
N-hydroxy-2-[1-(4-methoxyphenylsulfinyl)-(4-methylcyclohex-1-yl]-acetamide;
N-hydroxy-2-[1-(4-phenoxyphenylsulfinyl)-cyclohex-1-yl]-acetamide;
N-hydroxy-2-[4-(4-methoxyphenylsulfinyl)-*N*-CBZ-piperidin-4-yl)]-acetamide; and
N-hydroxy-2-[4-(4-methoxyphenylsulfinyl)-piperidin-4-yl)]-acetamide.
N-hydroxy-2-[4-(4-phenoxyphenylsulfinyl)-tetrahydropyran-4-yl]-acetamide;
4-[4-(4-chlorophenoxy)phenylsulfinylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 141.3-142.1 °C; IR (KBr) 3436 (br), 1649 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.67 (dm, J = 13.9 Hz, 1H), 1.79 (dm, J = 13.9 Hz, 1H), 1.97 (dm, J = 13.9 Hz, 1H), 2.24 (dm, J = 13.9 Hz, 1H), 2.97 (d, J = 13.7 Hz, 1H), 3.07 (d, J = 13.7 Hz, 1H), 3.33-3.54 (m_c, 2H), 3.69 (m_c, 2H), 7.12 (d, J = 8.9 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.9 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 8.87 (br s, 1H), 10.76 (s, 1H), ^{13}CNMR (DMSO-d_6) δ32.43 (t), 33.71 (t), 42.69 (s), 63.65 (t), 67.12 (t), 118.90 (d), 121.07 (d), 126.11 (d), 128.19 (s), 130.07 (d), 139.51 (s), 154.62 (s), 158.72 (s), 169.68 (s); FABHRMS Calcd. for $C_{19}H_{21}NSO_5Cl$ (M^+ + H): 410.0829 Found: 426.0825. Anal. Calcd. for $C_{19}H_{20}NSO_5Cl$: C, 55.68; H, 4.92; N, 3.42. Found: C, 55.70; H, 4.93; N, 3.64.
2-{4-[4-(4-chlorophenoxy)-phenylsulfinyl]-tetrahydropyran-4-yl } -*N*-hydroxyacetamide; and
N-hydroxy-2-[4-(4-phenoxyphenylsulfinyl)-tetrahydrothiopyran-1,1-dioxide-4-yl]-acetamide.

EXAMPLE 12

Preparation of Compounds of Formula Id

12A. Preparation of Id where n is 2, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Cyclopentyl, and R^5 is 4-Phenoxyphenyl

A solution of *N*-hydroxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide (45 mg) in methanol (4 ml) was treated with a solution of OXONE (260 mg) in water (2 ml). The mixture was stirred for 1 hour, then partitioned between methylene chloride and water. The organic layer was separated, and the solvent removed under reduced pressure. Preparative TLC on silica gel and elution with 10% methanol/methylene chloride gave *N*-hydroxy-2-[1-(4-phenoxyphenylsulfonyl)cyclopent-1-yl]-acetamide (20 mg), m/e = 393 (MNH_4^+, CIMS).

12B. Preparation of Id where n is 2, R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a mechanically stirred suspension of 4-[4-(4-chlorophenoxy)-phenylthiomethyl]tetrahydropyran-4-(N-hydroxycarboxamide) (59.8 g, 151.8 mmol) in 20% tetrahydrofuran-methanol (1570 ml) cooled to 5°C was added dropwise a solution of OXONE (152 g, 247 mmol) in water (1 litre), maintaining an internal temperature of 15-20°C. The mixture was stirred for 5.5 hours, and the mixture then partitioned between 30% ethyl acetate/water (3 litres). The aqueous layer was washed with ethyl acetate (2 x 300 ml), the combined ethyl acetate layers dried over magnesium sulfate, concentrated under reduced pressure, and the residue crystallized from the minimum amount of methylene chloride/hexanes,

to afford analytically pure 4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) as a white powder (54.2 g, 84%). mp 147.7-148.9 °C; IR (KBr) 3429 (br), 1636 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.70 (dm, *J* = 13.9, 2H), 1.96 (dm, *J* = 13.9 Hz, 2H), 3.38-3.48 (m, 2H), 3.58-3.68 (m, 2H), 3.58-3.68 (m, 2H), 3.66 (s, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H), 8.68 (d, *J* = 2.0 Hz, 1H), 10.54 (d, *J* = 2.0 Hz, 1H), ^{13}CNMR (DMSO-d_6) δ 32.83 (t), 41.70 (s), 61.02 (t), 63.19 (t), 118.01 (d), 121.71 (d), 128.73 (s), 130.08 (d), 130.19 (d), 135.20 (s), 153.83 (s), 160.86 (s), 168.96 (s); FABHRMS Calcd. for $C_{19}H_{20}NSO_6Cl$: 426.0778. Found: 426.0774. Anal. Calcd. for $C_{19}H_{20}NSO_6Cl$: C, 53.59; H, 4.73; N, 3.29. Found: C, 53.58; H, 4.70; N, 3.40.

12C. Preparation of Id where n is 2, R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 is hydrogen, R^4 is Benzyl, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a solution of 3-benzyl-4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid (316 mg, 0.63 mmol) and *N,N*-dimethylformamide catalyst (10 μL) in methylene chloride (6 ml) at 0°C was added oxalyl chloride (200 μL, 2.20 mmol) dropwise over 10 minutes. The mixture was warmed to room temperature over 1 hour, the partial slurry stirred an additional 8 hours, and concentrated *in vacuo* until the theoretical mass of the acid chloride was obtained. This mixture was dissolved in methylene chloride (8 ml), cooled to 0°C, and a neat solution of *N,O*-bis(trimethylsilyl)hydroxylamine (0.56 g, 3.15 mmol) added dropwise over 5 minutes. The mixture was immediately warmed to room temperature, stirred for 48 hours, and recooled to 0°C. To this solution was added aqueous 1M hydrochloric acid (5 ml, 150 mmol), and the solution stirred for an additional 30 minutes, partitioned between ethyl acetae (150 ml) and brine (50 ml). The organic layer was dried over magnesium sulfate, concentrated *in vacuo*, chromatographed over silica gel, eluted with 4% methanol/methylene chloride) to afford 280 mg (86%) of 3-benzyl-4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarbamide) hydroxamic acid. mp 108-113°C; IR (KBr) 3422 (br), 1653 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.76-1.86 (m, 1H), 2.08-2.27 (m, 2H), 2.34 (dm, *J* = 13.8 Hz, 1H), 2.91 (dd, *J* = 16.5, 7.2 Hz, 1H), 3.17 (dd, *J* = 16.4, 4.0 Hz, 1H), 3.19-3.23 (tm, *J* = 9.0 Hz, 1H), 3.43 (td, *J* = 11.9, 2.4 Hz, 2H), 6.65-6.72 (m, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.98-7.04 (m, 3H), 7.30 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 31.76 (t), 34.23 (t), 47.30 (s), 64.07 (t), 64.66 (t), 72.68 (d), 117.50 (d), 121.64 (d), 126.47 (d), 127.96 (d), 128.53 (d), 130.31 (d), 130.69 (d), 132.91 (s), 137.83 (s), 153.34 (s), 162.12 (s), 171.30 (s); FABMS (M^+ +H): 516; Anal. Calcd. for $C_{26}H_{26}NSO_6Cl$: C, 60.52; H, 5.08; N, 2.71. Found: C, 60.45; H, 5.10; N, 2.55.

12D. Preparation of Id where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 12C above, but replacing 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) with other compounds of Formula Iba, the following compounds of Formula Id where n is 2 were prepared:

4-[4-(4-fluorophenoxy)phenylsulfonylmethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 153.1-153.9 °C; IR (KBr) 3434 (br), 1636 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.87 (ddd, *J* = 13.6, 8.8, 4.0 Hz, 2H), 2.22 (dm, *J* = 13.6 Hz, 2H), 3.52-3.78 (m, 4H), 7.00-7.16 (m, 6H), 7.84 (d, *J* = 8.9 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 33.12 (t), 42.19 (s), 62.52 (t), 63.96 (t), 116.88 (dd, J_{C-F} = 21.3 Hz), 117.30 (d), 121.97 (dd, J_{C-F} = 8.4 Hz), 130.18 (s), 134.21 (d), 150.66 (d, J_{C-F} = 2.6 Hz), 159.73 (d, J_{C-F} = 243.8 Hz), 162.61 (s), 169.73 (s); FABMS (M^+ + H): 410. Anal. Calcd. for $C_{19}H_{20}NSO_6F$: C, 55.74; H, 4.92; N, 3.42. Found: C, 55.45; H, 4.91; N, 3.38.

4-[4-(4-bromophenoxy)phenylsulfonylmethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 150.1-151.0 °C; IR (KBr) 3432 (br), 1636 cm^{-1}; ^{1}HNMR ($CDCl_3$; NH and OH not observed) ∂ 1.87 (ddd, *J* = 13.6, 8.7, 3.9 Hz, 2H), 2.12 (dm, *J* = 13.6 Hz, 2H), 3.52 (s, 2H), 3.62-3.80 (m, 4H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ 33.10 (t), 42.16 (s), 62.49 (t), 63.93 (t), 117.66 (s), 117.83 (d), 121.93 (d), 130.20 (d), 133.17 (d), 134.61(s), 154.13 (s), 161.79 (s), 169.53 (s); FABHRMS Calcd. for $C_{19}H_{20}NSO_6Br$ (M^+ + H): 470.0273. Found: 470.0268. Anal. Calcd. for $C_{19}H_{20}NSO_6Br$: C, 48.51; H, 4.28; N, 2.98. Found: C, 48.29; H, 4.02; N, 2.94.

3-(4-benzoylphenylsulfonyl)-2,2-dimethyl-N-hydroxypropionamide;

3-[4-(4-chlorophenoxy)phenylsulfonyl]-2,2-dimethyl-*N*-hydroxypropionamide: mp 154.9-156.1 °C; ^{1}HNMR ($CDCl_3$) δ 1.45 (s, 6H), 3.48 (s, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H); FABMS (M^+ +H): 384.0. Anal. Calcd. for $C_{17}H_{18}NSO_5Cl$: C, 53.19; H, 4.73; N, 3.65. Found: C, 52.98; H, 4.69; N, 3.73.

4-(4-phenoxyphenylsulfonylmethyl)-tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 141.8-142.9 °C; IR (KBr) 3432 (br), 1636 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.74 (ddd, *J* = 13.8, 10.0, 3.9 Hz, 2H), 1.98 (dm, *J* = 13.8 Hz, 2H), 3.45 (m_c, 2H), 3.64 (m_c, 2H), 3.65 (s, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 8.68 (s, 1H), 10.52 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 32.87 (t), 41.76 (s), 61.19 (t), 63.28 (t), 117.71 (d), 119.99 (d), 124.91 (d), 130.04 (d), 130.34 (d), 134.85 (s), 154.85 (s), 161.39 (s), 168.97 (s); FABHRMS Calcd. for $C_{19}H_{22}NSO_6$ (M^+ + H): 392.1168. Found: 392.1162. Anal. Calcd. for $C_{19}H_{21}NSO_6.0.5H_2O$: C,

56.99; H, 5.54; N, 3.50. Found: C, 57.06; H, 5.35; N, 3.93.

4-[4-(4-thiophen-2-yl)phenoxyphenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 172.2-176.5 °C; IR (KBr) 3428 (br), 1636 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.72 (dm, *J* = 14.5 Hz, 2H), 1.99 (dm, *J* = 14.5 Hz, 2H), 3.46 (m_c, 2H), 3.65 (m_c, 2H), 3.66 (s, 2H), 7.14 (dd, *J* = 4.9, 3.6 Hz,1H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.9 Hz, 2H), 7.48 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.52 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 8.68 (s, 1H), 12.58 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 32.89 (t), 41.78 (s), 61.20 (t), 63.28 (t), 117.88 (d), 120.55 (d), 123.66 (d), 125.56 (d), 127.34 (d), 128.45 (d), 130.07 (d), 130.62 (s), 135.04 (s), 142.45 (s), 154.30 (s), 161.16 (s), 169.03 (s); FABHRMS Calcd. for $C_{23}H_{24}NS_2O_6$ (M^+ + H): 474.1045. Found: 474.1050. Anal. Calcd. for $C_{23}H_{23}NS_2O_6$: C, 58.33; H, 4.90; N, 3.00. Found: C, 58.18; H, 4.84; N, 3.19.

4-[4-(4-thiophen-3-yl)phenoxyphenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 183.5-184.4 °C; IR (KBr) 3432 (br), 1636 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.72 (m_c, 2H), 1.98 (m_c, 2H), 3.48 (m_c, 2H), 3.65 (m_c, 4H), 7.18 (m_c, 4H), 7.55 (dd, *J* = 5.1 Hz, 1H), 7.62 (d, *J* = 4.9, 3.7 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.86 (m_c, 3H), 8.69 (s, 1H), 10.58 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 32.88 (t), 41.79 (s), 61.19 (t), 63.28 (t), 117.71 (d), 120.42 (d), 120.81 (d), 126.09 (d), 127.10 (d), 127.97 (d), 130.06 (d), 132.10 (s), 134.89 (s), 140.54 (s), 153.86 (s), 168.85 (s); FAB-HRMS Calcd. for $C_{23}H_{24}NS_2O_6$ (M^+ + H): 474.1045. Found: 474.1049. Anal. Calcd. for $C_{23}H_{23}NS_2O_6.0.75H_2O$: C, 56.72; H, 5.07; N, 2.88. Found: C, 56.74; H, 4.78; N, 3.22.

3,3-dimethyl-3-[(4-chlorophenoxy)phenylsulfonyl]-*N*-hydroxypropionamide;

{4-[4-(4-benzo[b]thiophen-2-yl-phenoxy)phenylsulfonyl)-tetrahydropyran-4-yl]-*N*-hydroxyacetamide;

2-{4-[4-(phenylmethyl)phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;

2-{4-[4-(4-chlorophenoxy)phenylsulfonyl]tetrahydropyran-4-yl}-*N*-hydroxyacetamide; and

2-{4-[4-(4-bromophenoxy)phenylsulfonyl]tetrahydropyran-4-yl}-*N*-hydroxyacetamide.

12E. Preparation of Id where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 12A or 12B above, but replacing *N*-hydroxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide with other compounds of Formula Id where n is 0, the following compounds of Formula Id where n is 2 are prepared, for example;

4-(4-phenoxyphenylsulfonylmethyl)tetrahydropyran-4-(*N*-hydroxycarboxamide);

4-[4-(4-fluorophenoxy)phenylsulfonylmethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide);

4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]piperidine-4-(*N*-hydroxycarboxamide);

4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-methylpiperidine-4-(*N*-hydroxycarboxamide);

4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-cyclopropylmethylpiperidine-4-(*N*-hydroxycarboxamide);

4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-acetylpiperidine-4-(*N*-hydroxycarboxamide);

4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-(3-pyridyl)-piperidine-4-(*N*-hydroxycarboxamide);

4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-(3-pyridoyl)-piperidine-4-(*N*-hydroxycarboxamide);

N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide;

N-hydroxy-2-[4-(4-methoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide;

2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-*N*-CBZ-piperidin-4-yl}-*N*-hydroxyacetamide;

2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide;

N-hydroxy-2-[4-(4-methoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide;

N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide;

2-benzyl-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-propionamide;

3-benzyl-*N*-hydroxy-3-(3-methoxyphenylsulfonyl)-propionamide;

3-benzyl-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-propionamide;

3-benzyl-*N*-hydroxy-3-[(4-phenylthiophenyl)sulfonyl]-propionamide;

3-benzyl-*N*-hydroxy-3-(phenylsulfonyl)-propionamide;

3-benzyl-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide;

3-benzyl-3-[(4-biphenyl)sulfonyl]-*N*-hydroxypropionamide;

3-benzyl-*N*-hydroxy-3-(2-naphthylsulfonyl)-propionamide;

3-benzyl-*N*-hydroxy-3-(4-methoxystyrylphenylsulfonyl)-propionamide;

3-(cyclopentylmethyl)-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-propionamide;

3-(cyclopentylmethyl)-*N*-hydroxy-2-isopropyl-3-(4-methoxyphenyl-sulfonyl)-propionamide;

3-ethyl-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-2-methylpropionamide;

3,3-dimethyl-*N*-hydroxy-(4-methoxyphenylsulfonyl)-propionamide;

N-hydroxy-2-[1-(4-methoxyphenylsulfonyl)-cyclopent-1-yl]-acetamide;

N-hydroxy-2-[1-(4-methoxyphenylsulfonyl)-(4-methylcyclohex-1-yl]-acetamide;

N-hydroxy-2-[1-(4-phenoxyphenylsulfonyl)-cyclohex-1-yl]-acetamide;

N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydropyran-4-yl]-acetamide;

2-{4-[4-(4-chlorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-N-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide; and
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydrothiopyran-1,1-dioxide-4-yl]-acetamide.

12F. Preparation of Id where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 12A above, but replacing *N*-hydroxy-2-[1-(4-phenoxyphenylthio)-cyclopent-1-yl]-acetamide with other compounds of Formula Id where n is 0, other compounds of Formula Id where n is 2 are prepared.

EXAMPLE 13

Preparation of Compounds of Formula I where Y is *tert*-BuONH-

13A. Preparation of Ic where n is 2, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Tetrahydropyran, and R^5 is 4-Phenoxyphenyl

To a cooled solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetamide (14.1 g, 33.9 mmol) in methanol (340 ml) was added a solution of OXONE (33.9 g) in water (170 ml). The reaction mixture was stirred for 5 hours at room temperature, concentrated to half the original volume under reduced pressure, and the residue then partitioned between ethyl acetate and water. The solvent was removed from the ethyl acetate extracts under reduced pressure. The residue chromatographed on silica gel, eluting with 10% methanol/methylene chloride, to give *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydropyran-4-yl]-acetamide as a white foam.

13B. Preparation of Ic where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached are *N*-BOC-Piperidine, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylthiomethyl)-*N*-BOC-piperidin-4-yl]-carboxamide (4.96 g, 9.03 mmol) in anhydrous methylene chloride (70 ml) cooled to 0°C, was added 60% 3-chloroperoxybenzoic acid (4.96 g). After the resulting mixture was allowed to warm to room temperature over 30 minutes and stirred for 5 minutes, 13.6M aqueous methyl sulfide (1 ml, 13.62 mmol) was added in one portion. The mixture was stirred 10 minutes, partitioned with saturated aqueous sodium bicarbonate (2 x 50 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Chromatography over silica gel, and eluting with 25% ethyl acetate/hexanes, gave *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-*N*-BOC-piperidin-4-yl]-carboxamide as a white foam (4.70 g, 90%). ^{1}HNMR ($CDCl_3$) δ 1.31 (s, 9H), 1.46 (s, 9H), 1.59 (m_c, 2H), 2.18 (m_c, 2H), 3.42 (m_c, 2H), 3.45 (s, 2H), 3.62 (m_c, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 8.44 (br s, 1H).

13C. Preparation of Ic where n is 2 and Y is *tert*-BuONH-, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 13B above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylthiomethyl)-*N*-BOC-piperidin-4-yl]-carboxamide with other compounds of Formula Ib, the following compound of Formula Ic where n is 2 and Y is *tert*-BuONH- was prepared:

N-tert-butoxy-4-[4-(4-pyridyloxy)phenylsulfonylmethyl]-tetrahydropyran-carboxamide: IR (KBr) 3434, 1684 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.33 (s, 9H), 2.01 (m_c, 2H), 2.24 (m_c, 2H), 3.55 (s, 2H), 3.79 (m_c, 4H), 6.93 (d, *J* =6.3 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 8.38 (s, 1H), 8.57 (d, *J* = 6.3 Hz, 2H); FABHRMS Calcd. for $C_{22}H_{28}N_2SO_6$ (M^+ + H) 449.1746. Found: 449.1757.
N-tert-butoxy-4-[4-(5-chloro-2-pyridyloxy)phenylsulfonylmethyl]-tetrahydropyran-carboxamide: mp (broad) 100.8-135.8 °C; IR (KBr) 3436 (br), 1684 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.20 (s, 9H), 1.72 (m_c, 2H), 2.03 (m_c, 2H), 3.48 (m_c, 2H), 3.67 (m_c, 2H), 3.76 (s, 2H), 7.23 (dd, *J* = 8.8, 0.5 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 8.03 (dd, *J* = 8.8, 2.7 Hz, 1H), 8.25 (dd, *J* = 2.7, 0.5 Hz, 1H), 8.30 (s, 1H), 10.32 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 26.66 (q), 33.09 (t), 42.37 (s), 61.03 (t), 63.36 (t), 80.64 (s), 113.89 (d), 121.38 (d), 126.33 (s), 129.53 (d), 137.00 (s), 140.34 (d), 145.74 (d), 157.87 (s), 160.66 (s), 171.25 (s); FABHRMS Calcd. for $C_{22}H_{28}N_2SO_6Cl$ (M^+ + H): 483.1357. Found: 483.1354. Anal. Calcd. for $C_{22}H_{27}N_2SO_6Cl$: C, 54.71; H, 5.63; N, 5.80. Found: C, 54.46; H, 5.60; N, 5.98.
N-tert-butoxy-3-[4-(5-chloro-2-pyridyloxy)phenylsulfonyl]-2,2-dimethyl-propionamide: mp (broad) 64.5-70.5 °C; ^{1}HNMR (DMSO-d_6) δ 1.19 (s, 9H), 1.29 (s, 6H), 3.65 (s, 2H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 8.04 (dd, *J* = 8.8, 2.7 Hz, 1H), 8.26 (d, *J* = 2.7 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.01 (q), 26.47 (q), 40.74 (s), 63.03 (t), 80.79 (s), 113.91 (d), 121.38 (d), 126.32 (s), 129.35 (d), 130.66 (s), 140.36

(d), 145.75 (d), 157.72 (s), 160.68 (s), 173.14 (s); FABHRMS Calcd. for $C_{20}H_{26}N_2SO_5Cl$ (M^+ + H): 441.1251. Found: 441.1248. Anal. Calcd. for $C_{20}H_{25}N_2SO_5Cl$: C, 54.48; H, 5.71; N, 6.35. Found: C, 54.37; H, 5.69; N, 6.57.

13D. Preparation of Ic where n is 2 and Y is *tert*-BuONH-, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 13A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylthio)-tetrahydropyran-4-yl]-acetamide with other compounds of Formula Ib, the following compounds of Formula Ic where n is 2 and Y is *tert*-BuONH-were prepared;

N-tert-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-tert-butoxy-2-[4-(4-methoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide;
N-tert-butoxy-2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-piperidin-4-yl}-acetamide;
N-tert-butoxy-2-[4-(4-methoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide;
N-tert-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide;
2-benzyl-*N-tert*-butoxy-3-(4-methoxyphenylsulfonyl)-propionamide;
3-benzyl-*N-tert*-butoxy-3-(3-methoxyphenylsulfonyl)-propionamide;
3-benzyl-*N-tert*-butoxy-3-(4-methoxyphenylsulfonyl)-propionamide;
3-benzyl-*N-tert*-butoxy-3-[(4-phenylthiophenyl)sulfonyl]-propionamide;
3-benzyl-*N-tert*-butoxy-3-(phenylsulfonyl)-propionamide;
3-benzyl-*N-tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide;
3-benzyl-*N-tert*-butoxy-3-[(4-biphenyl)sulfonyl]-propionamide;
3-benzyl-*N-tert*-butoxy-3-(2-naphthylsulfonyl)-propionamide;
3-benzyl-*N-tert*-butoxy-3-(4-methoxystyrylphenylsulfonyl)-propionamide;
N-tert-butoxy-3-(cyclopentylmethyl)-3-(4-methoxyphenylsulfonyl)-propionamide;
N-tert-butoxy-3-(cyclopentylmethyl)-2-isopropyl-3-(4-methoxyphenylsulfonyl)-propionamide;
N-tert-butoxy-3-ethyl-2-methyl-3-(4-methoxyphenylsulfonyl)-propionamide;
N-tert-butoxy-3,3-dimethyl-(4-methoxyphenylsulfonyl)-propionamide;
N-tert-butoxy-2-[1-(4-methoxyphenylsulfonyl)-cyclopent-1-yl]-acetamide;
N-tert-butoxy-2-[1-(4-methoxyphenylsulfonyl)-(4-methylcyclohex-1-yl]-acetamide;
N-tert-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-cyclohexanone-4-yl]-acetamide ethylene ketal;
N-tert-butoxy-2-[1-(4-phenoxyphenylsulfonyl)-cyclohex-1-yl]-acetamide;
N-tert-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydropyran-4-yl]-acetamide;
N-tert-butoxy-2-{4-[4-(4-chlorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-acetamide;
N-tert-butoxy-2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-acetamide;
N-tert-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydrothiopyran-1,1-dioxide-4-yl]-acetamide;
N-tert-butoxy-2-(4-methoxyphenylsulfonyl)-cyclohexanecarboxamide; and
N-tert-butoxy-*trans*-2-(4-methoxyphenylsulfonyl)-cyclopentanecarboxamide.

13E. Preparation of Ic where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 13A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylthio)-*N*-CBZ-piperidin-4-yl)]-acetamide with other compounds of Formula Ib, other compounds of Formula Ic where n is 2 and Y is *tert*-BuONH- are prepared.

EXAMPLE 14

Preparation of Compounds of Formula Ic where Y is *tert*-BuONH-

14A. Preparation of Ic where n is 2, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Piperidine and R^5 is 4-Phenoxyphenyl

To a solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide (1.2 g, 2.1 mmol) in ethanol (21 ml) was added 10% palladium on carbon (1 g) and ammonium formate (6.7 g), and the mixture refluxed for 1 hour. The mixture was filtered through Celite, the filter cake washed with ethanol (150 ml) followed by 10% methanol in methylene chloride (150 ml). Solvent was removed from the filtrate under reduced pressure and the residue was dissolved in hot ethyl acetate. Filtration, concentration of the filtrate, followed by silica gel chromatography and elution with 10% methanol/methylene chloride gave *N*-tert-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide as a colorless oil.

14B. Preparation of Ic where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 14A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide with other *N*-CBZ protected compounds of Formula I, other compounds of Formula I where n is 2 and Y is *tert*-BuONH- are prepared.

EXAMPLE 15

Preparation of Compounds of Formula Id where Y is HONH-

15A. Preparation of Id where n is 2, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Piperidine, and R^5 is 4-Phenoxyphenyl

A solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperid-4-yl)]-acetamide (27 mg, 0.05 mmol) in dichloroethane (2 ml) was cooled to -20°C, and saturated with hydrochloric acid gas for 30 minutes. The reaction vessel was then sealed and the solution stirred for two days at 25°C. Solvent was removed from the reaction mixture under reduced pressure, and the residue dissolved in 50% methanol in methylene chloride. Addition of hexane precipitated *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide, m/e = 391 (MH^+, FAB).

15B. Preparation of Id where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 15A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide with other compounds of Formula Ic where Y is *tert*-BuONH-, the following compounds of Formula Id where n is 2 and Y is HONH- were prepared:

N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide, m/e = 525 (MH^+);
N-hydroxy-2-[4-(4-methoxyphenylsulfonyl)-*N*-CBZ-piperidin-4-yl)]-acetamide, m/e = 463 (MH^+, FAB);
2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide, m.p. 196-197°C;
2-{4-[4-(4-chlorophenoxy)phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide, m.p. 200-201°C;
2-{4-[4-(4-chlorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide: mp 135.7-136.1 °C; ^{1}HNMR ($CDCl_3$) δ 1.60 (m_c, 2H), 1.83 (m_c, 2H), 3.00 (s, 2H), 3.66 (m_c, 2H), 3.88 (m_c, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.25 (s, 1H), 9.49 (s, 1H); FABHRMS Calcd. for $C_{19}H_{20}NSO_6Cl$ (M^+ + H): 426.0778. Found: 426.0775. Anal. Calcd. for $C_{19}H_{20}NSO_6Cl$: C, 53.59; H, 4.73; N, 3.29. Found: C, 53.30; H, 4.67; N, 3.35.
2-[4-(4-cyclohexyloxyphenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide: m.p. 77-78°C;
N-hydroxy-2-[4-(4-methoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide, m/e = 329 (MH^+);
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide, m/e = 391 (MH^+);
2-benzyl-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-propionamide, m/e = 350.2 (MH^+);
3-benzyl-*N*-hydroxy-3-(3-methoxyphenylsulfonyl)-propionamide, m/e = 350.2 (MH^+);
3-benzyl-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-propionamide, m/e = 350.2 (MH^+);
3-benzyl-*N*-hydroxy-3-[(4-phenylthiophenyl)sulfonyl]-propionamide, m/e = 427 (MH^+);
3-benzyl-*N*-hydroxy-3-(phenylsulfonyl)-propionamide, m/e = 320 (MH^+);
3-benzyl-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide, m/e = 412.2 (MH^+);
3-benzyl-*N*-hydroxy-3-[(4-biphenyl)sulfonyl]-propionamide; m/e = 395 (MH^+);
3-benzyl-*N*-hydroxy-3-(2-naphthylsulfonyl)-propionamide, m/e = 370.1 (MH^+);
3-benzyl-*N*-hydroxy-3-[(4-methoxystyrylphenylsulfonyl]-propionamide, m/e = 452.2 (MH^+);
3-(cyclopentylmethyl)-*N*-hydroxy-3-(4-methoxyphenylsulfonyl)-propionamide, m/e = 342 (MH^+);
3-(cyclopentylmethyl)-*N*-hydroxy-2-isopropyl-3-(4-methoxyphenylsulfonyl)-propionamide;
3-ethyl-*N*-hydroxy-2-methyl-3-(4-methoxyphenylsulfonyl)-propionamide, m/e = 301 (MH^+);
3,3-dimethyl-3-(4-methoxyphenylsulfonyl)-*N*-hydroxypropionamide, elemental analysis: C_1H_1N;
N-hydroxy-2-[4-(4-methoxyphenylsulfonyl)-cyclopent-1-yl]-acetamide, m/e = 313 (MH^+);
N-hydroxy-2-[4-(4-methoxyphenylsulfonyl)-(4-methylcyclohex-1-yl]-acetamide, m/e = 341 (MH^+);
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)cyclohex-1-yl]-acetamide, m/e = 389 (MH^+);
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydropyran-4-yl]-acetamide, m.p. 88.5-90°C, m/e = 391 (MH^+);
2-{ 4-[4-(4-chlorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide;
2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide, m.p. 91-95°C;
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)tetrahydrothiopyran-1,1-dioxide-4-yl]-acetamide, m/e = 440.1 (MH^+);
N-hydroxy-*trans*-2-(4-methoxyphenylsulfonyl)-cyclopentanecarboxamide, m/e = 313 (MH^+);
N-hydroxy-*trans*-2-(4-methoxyphenylsulfonyl)-cyclohexanecarboxamide, m/e = 327 (MH^+); and

2-benzyl-*N*-hydroxy-*trans*-2-(4-methoxyphenylsulfonyl)-cyclopentane-carboxamide, m/e = 390 (MH^+, FABMS).

15C. Preparation of Id where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 15A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide with other compounds of Formula Ic where Y is *tert*-BuONH-, other compounds of Formula Id where n is 2 and Y is HONH-are prepared, for example:

2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-*N*-CBZ-piperidin-4-yl}-*N*-hydroxyacetamide;
2-{1-methyl-4-[4-(4-chlorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide;
N-hydroxy-2-{1-methyl-4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-acetamide; and
2-{4-[4-(4-bromophenoxy)-phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide.

15D. Preparation of Id where n is 2, R^1 and R^2 are Hydrogen, R^3 and R^4 when taken together with the Carbon to which they are attached are Cyclohexanone, and R^5 is 4-Phenoxyphenyl

Following the procedure outlined in Example 15A, *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-cyclohexanone-4-yl]-acetamide ethylene ketal (400 mg) was prepared from the corresponding *N-tert*-butoxy precursor. The above product was dissolved in a 1:1 mixture of acetone and 1M hydrochloric acid (40 ml) and stirred at room temperature for 18 hours. The reaction was concentrated under reduced pressure and extracted with ethyl acetate. Silica gel chromatography using 10% methanol/methylene chloride gave 2-[4-(4-phenoxyphenylsulfonyl)cyclohexanone-4-yl]-*N*-hydroxyacetamide as a white solid: m.p. 106°C (dec), m/e = 404 (MH^+, FABMS).

15E. Preparation of Id where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached are Piperidine, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a sealed tube containing the free base *N-tert*-butoxy-2-{4-[4-(4-phenoxy)phenylsulfonylmethyl]-piperidin-4-yl}-carboxamide (780 mg, 1.62 mmol) in 1,2-dichloroethane (35 ml) at -30°C, was bubbled in gaseous hydrochloric acid until the saturation point was reached. The reaction vessel was then sealed and the solution stirred for two days. After the vessel was recooled to -30°C and opened, a stream of nitrogen gas bubbled through the solution, which was then warmed to room temperature. The mixture was concentrated to afford 2-{4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-piperidin-4-yl}-*N*-hydroxycarboxamide (747 mg, 100%). mp 166.7-176.2°C; ^{1}HNMR (CD_3OD) δ 2.39 (m_c, 2H), 3.12 (m_c, 2H), 3.36 (m_c, 2H), 3.63 (s, 2H), 7.12 (d, *J* = 8.9 Hz, 2H), 7.15 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H); FABMS (M^+ +H): 425.0; Anal. Calcd. for $C_{19}H_{21}N_2SO_5Cl.HCl.1.5\,H_2O$: C, 46.73; H, 4.33; N, 5.74. Found: C, 46.83; H, 4.66; N, 5.71.

15F. Preparation of Id where n is 2, varying R^1, R^2, R^3, R^4, and R^5

Similarly, following the procedures of Example 15E above, but replacing *N-tert*-butoxy-2-{4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-piperidin-4-yl)}-carboxamide with other compounds of Formula Ic where Y is *tert*-BuONH-, other compounds of Formula Id where n is 2 and Y is HONH- were prepared, for example:

2-{4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-1-(cyclopropylmethyl)piperidin-4-yl}-*N*-hydroxycarboxamide hydrochloride (1.30 g, 84%). mp 120.5-124.0 °C; IR (KBr) 3429 (br), 1582 cm^{-1}; ^{1}HNMR (CD_3OD) δ 0.40-0.50 (m, 2H), 0.73-0.81 (m, 2H), 1.12 (m_c, 1H), 2.18 (m_c, 2H), 2.41 (d, *J* = 14.8 Hz, 2H), 2.63 (d, *J* = 14.3 Hz, 2H), 3.03 (m_c, 2H), 3.10 (m_c, 2H), 3.60 (m_c, 3H), 7.13 (m_c, 4H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H); FABMS (M^+ +H): 479.1. Anal. Calcd. for $C_{23}H_{27}N_2SO_5Cl.HCl.H_2O$: C, 51.77; H, 5.09; N, 5.25. Found: C, 51.90; H, 5.53; N, 5.26.

2-{4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-*N*-hydroxy-1-nicotinoylmethylpiperidin-4-yl}-carboxamide hydrochloride (590 mg, 89%). mp 160.5 °C (effervescence); IR (KBr) 3426 (br), 1638 cm^{-1}; ^{1}HNMR (CD_3OD) δ 1.97 (m_c, 2H), 2.25 (m_c, 2H), 3.55 (m_c, 4H), 3.64 (s, 2H), 7.10 (d, *J* = 8.9 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 8.12 (m_c, 1H), 8.61 (d, *J* = 7.9 Hz, 2H), 8.92 (d, *J* = 5.5 Hz, 2H), 8.98 (br s, 1H); FABMS (M^+ +H): 530.0. Anal. Calcd. for $C_{25}H_{29}N_3SO_6Cl.HCl.0.5H_2O$: C, 51.38; H, 4.14; N, 7.19. Found: C, 51.80; H, 4.46; N, 7.25.

2-{4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-*N*-hydroxy-1-methansulfonylpiperidin-4-yl}-carboxamide hydrochloride (682 mg, 69%). mp 107.3-112.3 °C; ^{1}HNMR ($CDCl_3$) δ 1.95 (m_c, 2H), 2.40 (m_c, 2H), 2.79 (s, 3H), 3.12 (m_c, 2H), 3.42 (s, 2H), 3.51 (m_c, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.83 (d, *J* = 8.9 Hz, 2H); FABMS (M^+ +H): 503.2. Anal. Calcd. for $C_{20}H_{23}N_2S_2O_7Cl$: C, 47.76; H, 4.61; N, 5.57. Found: C, 47.32; H, 4.56; N, 5.52.

4-[4-(4-pyridyloxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) hydrochloride: mp 188-

197°C; IR (KBr) 3431, 1638 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.73 (m_c, 2H), 2.01 (dm, J =14.7 Hz, 2H), 3.43 (m_c, 2H), 3.65 (m_c, 2H), 3.78 (s, 2H), 7.56 (m_c, 4H), 8.02 (d, J = 8.7 Hz, 2H), 8.82 (d, J = 6.6 Hz, 2H), 10.64 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 33.01 (t), 39.78 (t), 61.13 (s), 63.26 (t), 114.48 (d), 121.81 (d), 130.87 (d), 138.41 (s), 144.92 (d), 156.14 (s), 168.4 (s), 168.8 (s); Anal. Calcd. for $C_{18}H_{21}N_2SO_6Cl.HCl.0.6\ H_2O$: C, 49.17; H, 5.09; N, 6.37. Found: C, 49.16; H, 5.03; N, 6.27.

4-[4-(5-chloro-2-pyridyloxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide): mp 141.9-142.7°C; IR (KBr) 3432, 1636 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.73 (m_c, 2H), 2.01 (dm, J = 14.7 Hz, 2H), 3.33 (s, 2H), 3.46 (m_c, 2H), 3.64 (m_c, 2H), 7.23 (dd, J = 8.7, 0.4 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.7, 2.7 Hz, 2H), 8.26 (dd, J = 2.7, 0.4 Hz, 1H), 8.69 (s, 1H), 10.62 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 32.89 (t), 41.81 (s), 60.96 (t), 63.26 (t), 113.88 (d), 121.32 (d), 126.31 (s), 129.58 (d), 136.93 (s), 140.33 (s), 145.74 (d), 157.82 (s), 160.69 (s), 169.02 (s); FABHRMS Calcd. for $C_{18}H_{19}N_2SO_6Cl$ (M^+ + H): 427.0731. Found: 427.0726. Anal. Calcd. for $C_{18}H_{19}N_2SO_6C1.0.5H_2O$: C, 49.49; H, 4.61; N, 6.41. Found: C, 49.54; H, 4.35; N, 6.47.

3-[4-(5-chloro-2-pyridyloxy)phenylsulfonyl]-2,2-dimethyl-*N*-hydroxypropionamide: mp 115.8-116.6 °C; IR (KBr) 3412 (br), 1644 cm^{-1}; ^{1}HNMR (CD_3OD) δ 1.38 (s, 6H), 3.58 (s, 2H), 7.13 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.89 (dd, J = 8.7, 2.7 Hz, 2H), 7.95 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 25.55 (q), 41.76 (s), 65.06 (t), 114.91 (d), 122.35 (d), 128.40 (s), 130.98 (d), 138.21 (s), 141.44 (d), 146.88 (d), 159.89 (s), 162.32 (s), 174.51 (s); FABHRMS Calcd. for $C_{16}H_{18}N_2SO_5Cl$ (M^+ + H): 385.0625. Found: 383.0625. Anal. Calcd. for $C_{16}H_{17}N_2SO_5Cl$: C, 49.94; H, 4.48; N, 7.28. Found: C, 49.58; H, 4.42; N, 7.30.

15G. Preparation of Id where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached are 1-Picolylpiperidine. and R^5 is 4-(4-Chlorophenoxy)-phenyl

A solution containing *N-tert*-butoxy-2-{4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-1-picolylpiperidin-4-yl}-carboxamide (324 mg, 0.566 mmol) in trifluoroacetic acid (5 ml) was heated to 30°C for 1.5 hours, cooled to room temperature, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (100 ml), washed with saturated sodium bicarbonate (2 x 30 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Chromatography over silica gel, eluting with 6% methanol/methylene chloride, yielded 2-{4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-1-picolylpiperidin-4-yl}-*N*- hydroxycarboxamide hydrochloride: mp 222.5-223.9°C; IR (KBr) 3436 (br), 1645 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 2.15 (m_c, 3H), 2.40 (m_c, 2H), 3.32 (m_c, 2H), 3.57 (m_c, 2H), 3.97 (m_c, 2H), 4.44 (m_c, 2H), 4.51 (m_c, 2H), 7.19 (m_c, 4H), 7.50 (d, J = 8.8 Hz, 2H), 7.87 (m_c, 3H), 8.49 (m_c, 1H), 8.85 (m_c, 1H), 8.99 (br s, 1H); FABMS (M^+ +H): 516.1. Anal. Calcd. for $C_{29}H_{34}N_3SO_5Cl.2HCl.0.5\ H_2O$: C, 50.22; H, 4.89; N, 7.03. Found: C, 50.17; H, 4.65; N, 7.00.

EXAMPLE 16

Preparation of Compounds of Formula Ih

16A. Preparation of Ie where R^1 , R^2 and R^3 are Hydrogen, and R^4 is Benzyl

To a cooled solution of 3-benzyl-3-(4-bromophenylthio)-propionic acid in methanol (50 ml) was added a solution of OXONE (8 g) in water (50 ml). The reaction mixture was stirred for 2 hours at room temperature, and then partitioned between methylene chloride and water. The solvent was removed from the organic layer under reduced pressure, to give 3-benzyl-3-(4-bromophenylsulfonyl)-propionic acid, as a crystalline solid.

16B. Preparation of If where R^1 , R^2 and R^3 are Hydrogen, and R^4 is Benzyl

1. A solution of 3-(4-bromophenyl)sulfonyl-4-benzylpropionic acid (200 mg, 0.52 mmol), phenylboronic acid (127 mg, 1.04 mmol), and tetrakis(triphenylphospine)palladium(0) (24 mg, 0.021 mmol) in a 1:1 mixture of ethanol and benzene (5 ml) was heated to reflux temperature with stirring. A solution of 2M sodium carbonate (1 ml) was added to the reaction mixture, and stirring continued at reflux for approximately 2 hours. The mixture was cooled and then partitioned between ethyl acetate and water. The solvent layer was washed with brine, dried over magnesium sulfate, filtered, and solvent removed under reduced pressure. The residue was chromatographed, eluting with 7% methanol/methylene chloride, to yield 3-(4-biphenyl)-sulfonyl-4-benzylpropionic acid. ^{1}HNMR ($CDCl_3$): 7.75 ppm (m, 14H); 3.42 ppm (dd, 1H); 2.82 ppm (dd, 1H); 2.77 ppm (dd, 1H); 2.51 ppm (dd, 1H).

16C. Preparation of Ih where R^1, R^2, and R^3 are Hydrogen and R^4 is Benzyl

The 3-(4-biphenyl)sulfonyl-4-benzylpropionic acid, prepared as shown above, was then converted to 3-(4-biphenyl)sulfonyl-4-benzyl-*N*-hydroxypropionamide, m.p. 65°C (shrinks with decomposition) as described in Examples 10A.

16D. Preparation of Ifb where R^1 and R^2 Together with the Carbon to which they are attached represent Tetrahydropyran-4-yl, R^3 and R^4 are Hydrogen, R^5 is 4-(Thiophen-2-yl)phenoxyphenyl

1. To a mechanically stirred suspension of 4-[4-(4-bromophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid (5.50 g, 13.0 mmol) in 20% tetrahydrofuran/methanol (135 ml) cooled to 15°C, was added a solution of OXONE (13.0 g, 21.2 mmol) in water (86 ml) dropwise, maintaining an internal temperature of 15-20°C. The mixture was stirred for 12 hours and dissolved in 40% ethyl acetate/water (1200 ml). The layers were partitioned, and the water layer back extracted using ethyl acetate (2 x 300 ml). The combined ethyl acetate layers were dried ($MgSO_4$), concentrated, and the residue crystallized from the minimum amount of methylene chloride/hexanes to afford 4-[4-(4-bromophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid as a white powder, which was used without further purification (5.00 g, 84%).

2. To a solution of 4-[4-(4-bromophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid (1.10 g, 2.42 mmol) of in *N, N*-dimethylformamide (15 ml) was added tetrakis(triphenylphosphine)-palladium(0) (108 mg), 2-thiophene boronic acid (857 mg, 6.70 mmol), followed by 2M aqueous sodium carbonate (2.7 ml, 5.4 mmol). The reaction was heated to reflux for 10 hours, cooled to room temperature, and the mixture partitioned between methylene chloride (100 ml) and 1N aqueous hydrochloric acid (20 ml). The aqueous layer was back extracted with methylene chloride (100 ml), and the combined organic layers dried ($MgSO_4$), the residue chromatographed over 100 g of silica gel (eluted with methylene chloride to 10% methanol/methylene chloride), and the resulting foam crystallized from the minimum amount of methylene chloride/hexanes to afford 4-[4-(4-(thiophen-2-yl)phenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid (1.04 g, 94%). mp 181.2-193.3°C; IR (KBr) 3432 (br), 1718.9 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.67 (ddd, J = 13.8, 9.4, 4.0 Hz, 2H), 1.95 (dm, J = 13.8 Hz, 2H), 3.47 (m_c, 2H), 3.67 (m_c, 2H), 3.68 (s, 2H), 7.14 (dd, J = 4.9, 3.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 7.50 (dd, J = 3.6, 1.2 Hz, 1H), 7.54 (dd, J = 4.9, 1.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 12.80 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 32.92 (t), 42.25 (s), 61.73 (t), 63.26 (t), 117.82 (d), 123.75 (d), 125.66 (d), 127.39 (d), 128.50 (d), 130.08 (d), 130.74 (s), 134.90 (s), 142.42 (s), 154.13 (s), 161.33 (s), 174.39 (s); FABHRMS Calcd. for $C_{23}H_{24}S_2O_6$ (M^+ + H): 459.0936. Found: 459.0936. Anal. Calcd. for $C_{23}H_{23}S_2O_6$: C, 60.24; H, 4.83. Found: C, 60.57; H, 4.90.

16E. Preparation of Ifb where R^1 and R^2 Together with the Carbon to which they are attached represent Tetrahydropyran-4-yl, R^3 and R^4 are Hydrogen, R^5 is 4-(Thiophen-3-yl)phenoxyphenyl

Similarly, following the above procedure, other compounds of Formula Ifb, were prepared, for example replacing 2-thiophene boronic acid with 3-thiophene boronic acid, 4-[4-(4-(thiophen-3-yl)phenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid was prepared: mp 206.6-212.4 °C; IR (KBr) 3430 (br), 1719 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.67 (m_c, 2H), 1.95 (m_c, 2H), 3.47 (m_c, 2H), 3.66 (m_c, 2H), 3.67 (s, 2H), 7.20 (m_c, 4H), 7.56 (dd, J = 5.0, 1.4 Hz, 1H), 7.64 (d, J = 5.0, 2.9 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.87 (m_c, 2H), 7.96 (s, 1H), 12.77 (s, 1H); ^{13}CNMR (DMSO-d_6) δ 32.92 (t), 40.38 (s), 61.19 (t), 63.26 (t), 117.66 (d), 120.54 (d), 120.87 (d), 126.04 (d), 127.07 (d), 127.96 (d), 130.02 (d), 132.00 (s), 134.66 (s), 140.45 (s), 160.80 (s), 174.32 (s); FABHRMS Calcd. for $C_{23}H_{23}S_2O_6$ (M^+ + H): 459.0936. Found: 459.0934. Anal. Calcd. for $C_{23}H_{22}S_2O_6.0.5H_2O$: C, 59.08; H, 4.96. Found: C, 58.82; H, 4.69.

16F. Catalytic Reduction of 4-[4-(4-bromophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid

A solution of 660 mg (1.45 mmol) of 4-[4-(4-bromophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid in 80% ethanol/tetrahydropyran (40 ml) was hydrogenated at atmospheric pressure for 14 hours using palladium on carbon catalyst, filtered over a celite pad washing with methylene chloride and concentrated *in vacuo* to afford 4-[4-phenoxyphenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid as a light orange solid (546 mg, 100%), which was taken directly into the next reaction without further purification: mp 162.5-165.3°C; IR (KBr) 3431 (br), 1727 cm^{-1}; ^{1}HNMR (DMSO-d_6) δ 1.67 (ddd, J = 14.1, 10.0, 4.0 Hz, 2H), 1.95 (dm, J = 14.1 Hz, 2H), 3.47 (m_c, 2H), 3.65 (m_c, 2H), 3.66 (s, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.86 (d, J = 7.9 Hz, 2H), 12.74 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 32.88 (t), 42.26 (s), 61.75 (t), 63.26 (t), 117.64 (d), 120.11 (d), 125.03 (d), 130.04 (d), 130.39 (s), 134.69 (s), 154.69 (s), 161.53 (s), 174.39 (s); FABHRMS Calcd for $C_{19}H_{21}SO_6$ (M^+ + H): 377.1059. Found: 378.1064. Anal. Calcd. for $C_{19}H_{20}SO_6.0.75H_2O$: C, 58.52; H, 5.56. Found: C, 58.54; H, 5.19.

EXAMPLE 17

Preparation of Compounds of Formula Ij

17A. Preparation of Ii where R^1, R^2 and R^3 are Hydrogen, and R^4 is Benzyl

Thiophenol (80 mg) was stirred for 45 min with potassium hydride (40 mg) in *N,N*-dimethylformamide (1 ml) to produce a homogeneous solution of potassium thiophenolate. To this mixture was added 3-benzyl-3-(4-bromophenylsulfonyl)-propionic acid (100 mg) dissolved in *N,N*-dimethylformamide (1 ml) at room temperature. After stirring for 16 hours at 75°C the mixture was partitioned between aqueous citric acid and water, giving a product which was purified by preparative TLC to afford 3-benzyl-3-(4-phenylthiophenylsulfonyl)-propionic acid (30 mg).

17B. Preparation of Ij where R^1, R^2 and R^3 are Hydrogen, and R^4 is Benzyl

The 3-benzyl-3-(4-phenylthiophenylsulfonyl)-propionic acid, prepared as shown above, was then converted to 3-benzyl-3-(4-phenylthiophenylsulfonyl)-*N*-hydroxypropionamide as descibed in Example 10A.

EXAMPLE 18

Preparation of Compounds of Formula Ik

18A. Preparation of Ik where R^1, R^2 and R^3 are Hydrogen, and R^4 is Benzyl

A mixture of 3-benzyl-3-(4-bromophenylsulfonyl)-propionic acid (250 mg), *p*-methoxystyrene (0.1 ml), diisopropylethylemine (0.25 ml), palladium acetate (5 mg) and tri(o-methylphenyl)phosphine (16 mg) was stirred overnight at 80°C. The reaction mixture was dissolved in methylene chloride and washed with aqueous citric acid. Solvent was removed from the methylene chloride solution, and the residue chromatographed on silica gel (preparative TLC, eluting with 10% methanol/methylene chloride), to afford 3-benzyl-3-(4-styrylphenylsulfonyl)-propionic acid (21 mg).

18B. Preparation of Ik where R^1, R^2 and R^3 are Hydrogen, and R^4 is Benzyl

The 3-benzyl-3-(4-styrylphenylsulfonyl)-propionic acid, prepared as shown above, was then converted to 3-benzyl-3-(4-styrylphenylsulfonyl)-*N*-hydroxypropionamide, LSIMS m/e=452.2 $(M+H)^+$, as descibed in Example 10A.

EXAMPLE 19

Preparation of Compounds of Formula Il

Preparation of Il where n is 2, R^1 and R^2 together with the Carbon to which they are attached are Piperidine, R^2 and R^3 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl

Trifluoroacetic acid (4 ml) was added to a solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-*N*-BOC-piperidin-4-yl]-carboxamide (2 g, 3.64 mmol) dissolved in methylene chloride (4 ml). The reaction mixture was stirred for 1.3 hours and concentrated *in vacuo*. The crude salt residue was dissolved in ethyl acetate (150 ml), washed with saturated aqueous sodium bicarbonate (2 x 50 ml), dried over magnesium sulfate, concentrated *in vacuo*, to afford the free base, *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-piperidin-4-yl]-carboxamide (1.57 g, 90%). ^{1}HNMR ($CDCl_3$) δ 1.28 (s, 9H), 2.23 (m_c, 2H), 2.56 (m_c, 2H), 3.30 (m_c, 2H), 3.44 (m_c, 2H), 3.53 (m_c, 2H), 7.00 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 8.25 (br s, 1H), 8.48 (br s, 1H).

EXAMPLE 20

Preparation of Compounds of Formula Im

20A. Preparation of Im where n is 2, R is Ethoxycarbonylmethyl, R^1 and R^2 are Hydrogen, and R^5 is 4-Phenoxyphenyl

A solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide (750 mg) in *N, N*-dimethylformamide (10 ml) was treated with ethyl bromoacetate (0.2 ml) and potassium carbonate (600 mg). The mixture was stirred overnight at room temperature, and then partitioned between ethyl acetate and water. After drying, solvent was removed from the organic layer under reduced pressure to yield *N-tert*-butoxy-2- [4-(4-phenoxyphenyl-sulfonyl)-1-

(ethoxycarbonylmethyl)piperidin-4-yl]-acetamide, which was used in the next step without further purification.

20B. Preparation of Im where n is 2, R is Isopropyl, R^1 and R^2 are Hydrogen, and R^5 is 4-Phenoxyphenyl

To a solution of *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide (500 mg) in acetone (20 ml) was added 10% palladium on carbon (100 mg), and the mixture stirred under hydrogen for three days. The catalyst was filtered off, and solvent removed from the filtrate under reduced pressure. The residue was chromatographed on silica gel, eluting with 10% methanol/methylene chloride, to give *N-t*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(isopropyl)piperidin-4-yl)]-acetamide (300 mg).

20C. Preparation of Im where n is 2, varying R

Similarly, following the procedures of Example 20A above, but replacing ethyl bromoacetate with 3-picolyl chloride, *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(3-picolyl)piperidin-4-yl]-acetamide was prepared.

Similarly, following the procedures of Example 20A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)piperidin-4-yl)]-acetamide with *N-tert*-butoxy-2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-acetamide, and replacing ethyl bromoacetate with cyclopropylmethyl bromide, *N-tert*-butoxy-2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-1-(cyclopropylmethyl)-piperidin-4-yl}-acetamide was prepared.

Similarly, *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(acetamidocarbonylmethyl)piperidin-4-yl]-acetamide was prepared.

20D. Preparation of Im where n is 2, varying R

Similarly, following the procedures of Example 20A above, but optionally replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperid-4-yl)]-acetamide with other compounds of Formula Iy, and optionally replacing ethyl bromoacetate with other compounds of formula RX, where R is lower alkyl, cycloalkylalkyl, acyl, alkoxycarbonylalkyl, picoline, $-SO_2R^a$, where R^a is lower alkyl or $-NR^bR^c$, where R^b and R^c are independently hydrogen or lower alkyl; and the like, and X is chloro, bromo or iodo, other compounds of Formula Im were prepared:

N-tert-butoxy-2-[1-ethyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide;
N-tert-butoxy-2-[1-methyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide, m.p. 152-155°C;
N-tert-butoxy-2-[1-(2-methylpropyl)-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide;
N-tert-butoxy-2-[1-cyclopropylmethyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide;
N-tert-butoxy-2-[1-cyclopropylmethyl-4-[4-(4-chlorophenoxy)-phenylsulfonyl]-piperidin-4-yl]-acetamide; and
N-tert-butoxy-2-[1-acetyl-4-[4-(4-fluorophenoxy)phenylsulfonyl]-piperidin-4-yl]-acetamide.

20E. Preparation of Ic where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached is 1-CyclopropylmethylPiperidine, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a solution of the free base *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-piperidin-4-yl]-carboxamide (1.28 g, 2.66 mmol) dissolved in *N,N*-dimethylformamide (17 ml), was added cyclopropylmethyl bromide (0.26 ml, 2.66 mmol), followed by potassium carbonate (1.84 g, 13.3 mmol). After the reaction mixture was stirred for 20 hours, water was added (100 ml), and the aqueous solution extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried over magnesium sulfate, concentrated *in vacuo*. Chromatography over silica gel, and eluting with 25% ethyl acetate/hexanes, gave *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-1-(cyclopropyl)piperidin-4-yl]-carboxamide (1.30 g, 92%). ^{1}HNMR ($CDCl_3$) δ 0.10 (ddd, *J* = 5.6, 4.7, 4.6 Hz, 2H), 0.53 (ddd, *J* =8.7, 4.7, 4.5 Hz, 2H), 0.85 (m_c, 1H), 1.31 (s, 3H), 1.64 (m_c, 2H), 2.06 (m_c, 2H), 2.24 (m_c, 2H), 2.28 (d, *J* = 6.5 Hz, 2H), 2.67 (m_c, 4H), 3.50 (m_c, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 8.33 (br s, 2H); FABMS (M^+ +H): 535.2.

20F. Preparation of Ic where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached is 1-(3-Picolyl)piperidine, and R^5 is 4-(4-Chlorophenoxy)-phenyl

Similarly, following the procedures of Example 20E above, but replacing cyclopropylmethyl bromide with 1.25 equivalents of 3-picolyol chloride hydrochloride, *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-1-(3-picolyl)piperidin-4-yl]-carboxamide was prepared: mp 83.3-93.8°C; IR (KBr) 3436, 1661 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.31 (s, 9H), 2.00 (m_c, 2H), 2.24 (m_c, 2H), 2.55 (m_c, 4H), 3.48 (s, 2H), 3.53 (s, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 7.25 (dd, *J* = 7.6, 4.6 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.64 (brd, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H), 8.36 (br s, 1H), 8.52 (m, 2H); FABMS (M^+ +H): 572.0. Anal. Calcd. for $C_{29}H_{34}N_3SO_5Cl.0.5\ H_2O$: C, 59.03; H, 5.81; N, 7.12. Found: C,

59.37; H, 6.15; N, 7.98.

20G. Preparation of Ic where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached is 1-(Nicotinoyl)Piperidine, and R^5 is 4-(4-Chlorophenoxy)-phenyl

To a solution of the free base *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-piperidin-4-yl]-carboxamide (491 mg, 1.02 mmol) and *N,N*-diisopropylethylamine (444 mg, 2.55 mmol) in methylene chloride (2 ml) cooled to 0°C, was added nicotinyl chloride hydrochloride (219 mg, 1.27 mmol) in one portion. After the reaction mixture was stirred for 3 hours, water (30 ml) was added, and the aqueous solution extracted with ethyl acetate (2 x 60 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried over magnesium sulfate, concentrated *in vacuo*. Chromatography over silica gel, and eluting with 6% methanol/methylene chloride, afforded *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-1-(nicotinoyl)piperidin-4-yl]-carboxamide (233 mg, 39%). ^{1}HNMR ($CDCl_3$) δ 1.33 (s, 9H), 1.95 (m_c, 2H), 2.35 (m_c, 2H), 3.45 (m_c, 2H), 3.49 (s, 2H), 3.55 (m_c, 4H), 7.01 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.41 (m_c, 2H), 7.79 (m_c, 2H), 7.83 (d, J = 8.8 Hz, 2H), 8.69 (br s, 1H), 8.52 (m_c, 2H).

20H. Preparation of Ic where n is 2, R^3 and R^4 are Hydrogen, R^1 and R^2 when taken together with the Carbon to which they are attached is 1-(Methanesulfonyl)Piperidine, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a solution of the free base *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-piperidin-4-yl]-carboxamide (1.57 g, 3.26 mmol) in 67% methylene chloride/pyridine (16.5 ml) cooled to -78°C, was added a solution of methanesulfonyl chloride (0.51 ml, 6.53 mmol) in methylene chloride (2 ml). After the reaction mixture was stirred for 4 hours, 3N aqueous hydrochloric acid (25 ml) was added, and the aqueous solution extracted with ethyl acetate (2 x 60 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried over magnesium sulfate, concentrated *in vacuo*. Chromatography over silica gel, and eluting with 45% ethyl acetate/hexanes, afforded *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonylmethyl)-1-(methanesulfonyl)piperidin-4-yl]-carboxamide (1.16 g, 64%). ^{1}HNMR ($CDCl_3$) δ 1.33 (s, 9H), 2.05 (m_c, 2H), 2.37 (m_c, 2H), 2.79 (s, 3H), 3.23 (m_c, 2H), 3.43 (s, 2H), 3.47 (m_c, 2H), 7.01 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 8.9 Hz, 2H); FABMS (M^+ +H): 559.1.

EXAMPLE 21

Preparation of Compounds of Formula In

21A. Preparation of In where n is 2, R is Ethoxycarbonylmethyl, R^1 and R^2 are Hydrogen, and R^5 is 4-Phenoxyphenyl

The product from Example 20A, *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(ethoxycarbonylmethyl)piperidin-4-yl]-acetamide, was dissolved in dichloroethane (10 ml), cooled to 0°C, and saturated with hydrochloric acid gas. The reaction vessel was then sealed and the solution stirred for two days at 25°C. Solvent was removed from the reaction mixture under reduced pressure, and the residue purified by preparative TLC, eluting with 10% methanol/ methylene chloride, to give *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(ethoxycarbonylmethyl)piperidin-4-yl]-acetamide (420 mg), m/e = 477.1 (MH^+, FABMS).

21B. Preparation of In where n is 2, R is Isopropyl, R^1 and R^2 are Hydrogen, and R^5 is 4-Phenoxyphenyl

The product from Example 20B, *N-t*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(isopropyl)piperidin-4-yl)]acetamide, was reacted with hydrochloric acid gas as described above, to yield *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(isopropyl)piperidin-4-yl)]-acetamide (155 mg), m.p. 128°C, m/e = 432 (MH^+,EIMS).

21C. Preparation of In where n is 2, varying R

Similarly, following the procedures of Example 21A above, but replacing ethyl bromoacetate with 3-picolyl chloride, *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-1-(3-picolyl)piperidin-4-yl]-acetamide was prepared, m.p. 185-192°C (dec).

Similarly, following the procedures of Example 19A above, but replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide with *N-tert*-butoxy-2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-acetamide, and replacing ethyl bromoacetate with cyclopropylmethyl bromide, *N*-hydroxy-2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-1-cyclopropylmethylpiperidin-4-yl}-acetamide was prepared, m.p. 104-105°C.

Similarly, *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-1-acetamidocarbonylmethylpiperidin-4-yl]-acetamide was prepared.

21D. Preparation of In where n is 2, varying R

Similarly, following the procedures of Example 21A above, but optionally replacing *N-tert*-butoxy-2-[4-(4-phenoxyphenylsulfonyl)-piperid-4-yl)]-acetamide with other compounds of Formula Iy, and optionally replacing ethyl bromoacetate with other compounds of formula RX, where R is lower alkyl, cycloalkylalkyl, acyl, alkoxycarbonylalkyl, picoline, $-SO_2R^a$, where R^a is lower alkyl or $-NR^bR^c$, where R^b and R^c are independently hydrogen or lower alkyl; and the like, and X is chloro, bromo or iodo, other compounds of Formula In were prepared:

2-[1-ethyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-*N*-hydroxyacetamide, m.p. 182-183°C;
N-hydroxy-2-[1-methyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide, m.p. 152-155°C;
N-hydroxy-2-[1-(2-methylpropyl)-4-(4-phenoxyphenylsulfonyl)-piperid-4-yl]-acetamide, m.p. 226-227°C;
2-[1-cyclopropylmethyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide, m.p. 210-211°C;
2-[1-cyclopropylmethyl-4-[4-(4-chlorophenoxy)-phenylsulfonyl]-piperidin-4-yl]-*N*-hydroxyacetamide, m.p. 110-112°C; and
2-[1-acetyl-4-[4-(4-fluorophenoxy)phenylsulfonyl]-piperidin-4-yl]-*N*-hydroxyacetamide, m/e = 450 (MH^+).

EXAMPLE 22

Preparation of Compounds of Formula Iab

Preparation of Iab where R^5 is 4-phenoxyphenyl

4-Phenoxythiophenol (4.8 g) was stirred for 45 min with potassium hydride (0.98 g) in *N, N*-dimethylformamide (100 ml) to produce a homogeneous solution of potassium 4-phenoxythiophenolate. The lactone, (S)-3-carbobenzyloxyamino-2-oxetanone (5.3 g) (Arnold, L.D. *et al., J. Am. Chem. Soc.,* **107**, 7105 (1985)), dissolved in *N, N*-dimethylformamide (50 ml) was then added at room temperature. After stirring for 30 minutes the mixture was poured into water and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, and solvent removed under reduced pressure to give (*R*)-2-(benzyloxycarbonylamino)-3-(4-phenoxyphenylthio)-propionic acid (9.2 g). It can be used directly in the next step.

EXAMPLE 23

Preparation of Compounds of Formula Io

Preparation of Io where R^5 is 4-phenoxyphenyl

The above-prepared (*R*)-2-(benzyloxycarbonylamino)-3-(4-phenoxyphenylthio)-propionic acid was dissolved in methylene chloride (175 ml), cooled to 0°C, and treated with *O-(tert*-butyl)hydroxylamine hydrochloride (7.7 g), 4-methylmorpholine (9.4 ml), 1-hydroxybenzotriazole (2.8 g), and *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide (7.9 g). The mixture was allowed to warm to room temperature, stirred for 1.5 hours, then partitioned between methylene chloride and water. Solvent was removed from the organic phase under reduced pressure, and the residue purified by flash chromatography on silica gel, eluting with 0 to 50% ethyl acetate/hexane, to provide (*R*)-2-(benzyloxycarbonylamino)-*N-tert*-butoxy-3-(4-phenoxyphenylthio)-propionamide (7.4 g) as a white foam.

EXAMPLE 24

Preparation of Compounds of Formula Ip

Preparation of Ip where n is 2 and R^5 is 4-phenoxyphenyl

(*R*)-*N-tert*-butoxy-2-(benzyloxycarbonylamino)-3-(4-phenoxyphenylthio)-propionamide (1.5 mmol) was dissolved in methanol (140 ml), and a solution of OXONE (15 g) in water (50 ml) was added with vigorous stirring. The oxidation is usually complete within 2 hours. The mixture is then partitioned between methylene chloride and water. Solvent was removed from the dried organic phase under reduced pressure, to afford (*R*)-2-(benzyloxycarbonylamino)-*N-tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (8.3 g) in near-quantitative yield.

EXAMPLE 25

Preparation of Compounds of Formula Iq

Preparation of Iq where n is 2, R^1 is Hydrogen, R^2 is $-NR^6R^7$, in which R^6 is Hydrogen and R^7 is Benzyloxycarbonylamino, and R^5 is 4-phenoxyphenyl

A solution of (*R*)-2-(benzyloxycarbonylamino)-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (1.2 g) obtained from Example 16 in methylene chloride (5 ml) was diluted with trifluoroacetic acid (30 ml). The solution was allowed to stand overnight, and solvent was removed under reduced pressure. This residue was chromatographed on silica gel, eluting with 10% methanol/methylene chloride to give (*R*)-2-(benzyloxycarbonylamino)-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide (400 mg), m.p. 195-202°C.

EXAMPLE 26

Preparation of Compounds of Formula Ir

Preparation of Ir where n is 2 and R^5 is 4-phenoxyphenyl

(*R*)-2-(benzyloxycarbonylamino)-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (6.0 g) obtained from Example 17 was dissolved in ethanol (100 ml) and hydrogenated at 1 atmosphere in the presence of 10% palladium on carbon (6 g) for a period of 18 hours. The catalyst was filtered off and the solvent removed from the filtrate under reduced pressure to give (*R*)-2-amino-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide as a glass.

EXAMPLE 27

Preparation of Compounds of Formula Is

Preparation of Is where n is 2, R^1 is Hydrogen, R^2 is $-NR^6R^7$, in which R^6 and R^7 are both Hydrogen, and R^5 is 4-phenoxyphenyl

Similarly as in Example 25, (*R*)-2-amino-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (6.0 g) was dissolved in 1,2-dichloroethane (5 ml) and cooled to -20°C and bubbled for 20 minutes with hydrochloric acid gas in a pressure tube. The flask was then sealed and the mixture stirred overnight. The tube was cooled, vented, and allowed to warm. The solution was rinsed with methanol, the solvent removed from the filtrate under reduced pressure, triturated with 1:1 hexane/ethyl acetate (4 ml). The residue was filtered and dried to give (*R*)-2-amino-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide hydrochloride, m.p. 178-180°C (dec).

EXAMPLE 28

Preparation of Compounds of Formula It

Preparation of It where n is 2, R^1 is Hydrogen, R^2 is $-NR^6R^7$, in which R^6 is Hydrogen and R^7 is CBZ-(*S*)-Valinamido, and R^5 is 4-phenoxyphenyl

To a solution of (*R*)-2-amino-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (1.9 g) in methylene chloride (30 ml) was added CBZ-(*S*)-valine (1.6 g), 1-hydroxybenzotriazole (0.9 g), triethylamine (1 ml), and *N'*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide (1.3 g). After stirring overnight at room temperature, the solution was partitioned between methylene chloride and water, and after the organic layer was dried over magnesium sulfate, solvent was removed under reduced pressure to give (*R*)-*N*-*tert*-butoxy-2-(CBZ-valinamido)-3-(4-phenoxyphenylsulfonyl)-propionamide, which was used without further purification.

EXAMPLE 29

Preparation of Compounds of Formula Iu

Preparation of Iu where n is 2, R^1 is Hydrogen, R^2 is $-NR^6R^7$, in which R^6 is Hydrogen and R^7 is (*S*)-Valinamido, and R^5 is 4-phenoxyphenyl

A solution of (*R*)-*N*-*tert*-butoxy-2-(CBZ-valinamido)-3-(4-phenoxyphenylsulfonyl)-propionamide (prepared above) in a mixture of methanol (300 ml) and ethanol (100 ml) was stirred under hydrogen at 1 atmosphere with palladium on carbon catalyst (10% Pd, 4 g) for 3 hours. The mixture was filtered, and the filtrate evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-3% methanol in methylene chloride, to give (*R*)-*N*-*tert*-butoxy-2-valinamido-3-(4-phenoxyphenylsulfonyl)-propionamide (1.6 g).

EXAMPLE 30

Preparation of Compounds of Formula Iv

Preparation of Iv where n is 2, R^1 is Hydrogen, R^2 is $-NR^6R^7$, in which R^6 is Hydrogen and R^7 is (*S*)-Valinamido, and R^5 is 4-phenoxyphenyl

A solution of (*R*)-*N*-*tert*-butoxy-2-valinamido-3-(4-phenoxyphenylsulfonyl)-propionamide (1.6 g) in 1,2-dichloroethane (50 ml) was cooled to -20°C and bubbled for 15-20 minutes with hydrochloric acid gas in a pressure tube. The flask was then sealed and the mixture stirred for 24 hours. After cooling the tube was cautiously vented and its contents evaporated to yield a gum, which upon trituration with ethyl acetate gave a crude product as a white powder. This product was stirred overnight with 10% methanol/methylene chloride (20 ml) and filtered to remove impurities. This was repeated three times to give (*R*)-*N*-hydroxy-2-valinamido-3-(4-phenoxyphenylsulfonyl)-propionamide hydrochloride (760 mg), m.p. 214-217°C.

EXAMPLE 31

Preparation of Compounds of Formula Iw

Preparation of Iw where n is 2, Y is hydroxy or lower alkoxy, R^1 and R^2 when taken together with the carbon to which they are attached are Tetrahydropyan-4-yl, R^3 is hydrogen, and R^4 is Benzyl, and R^5 is 4-(4-Chlorophenoxy)phenyl

1. To a solution of 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-carboxylic acid methyl ester in 20% tetrahydrofuran-methanol (9.5 ml) was added dropwise a solution of OXONE (1.53 g, 2.49 mmol) in water (8 ml) while maintaining an internal temperature of 15-20°C. The mixture was stirred 2 hours and the mixture dissolved in 40% ethyl acetate/water (200 ml). The layers were partitioned, and the water layer back extracted using ethyl acetate (2 x 50 ml). The combined organic layers were dried over magnesium sulfate, concentrated, and the residue purified by preparative chromatography (20 x 40-1000 um plates), eluting with 50% ethyl acetate/hexanes) to afford 4-[4-(4-chlorophenoxy)phenyl-sulfonylmethyl]-tetrahydropyran-4-carboxylic acid methyl ester (460 mg, 71%). ^{1}HNMR ($CDCl_3$) δ 1.71-1.82 (m, 2H), 2.23 (dm, *J* = 13.6 Hz, 2H), 3.47 (s, 2H), 3.58-3.67 (m, 2H), 3.59 (s, 3H), 3.73-3.81 (m, 2H), 6.97-7.10 (m, 4H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 8.7 Hz, 2H).

2. Lithium diisopropylamide was prepared by the addition of 2.5M *N*-butyl lithium (610 μL, 1.53 mmol) in hexanes to a solution of diisopropylamine (200 μL, 1.53 mmol) in tetrahydrofuran (3 ml) at 0°C and stirring for 20 minutes. Then a solution of 4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid methyl ester (540 mg, 1.27 mmol) in tetrahydrofuran (1 ml) was added to the solution of lithium diisopropylamide at -78°C, and stirred for an additional 60 minutes. Benzyl bromide (181 μL, 1.53 mmol) of was added to the mixture, stirred for an 50 minutes, warmed to room temperature over 30 minutes, and stirred for an additional 3 hours. The mixture was then diluted with 0.1M aqueous hydrochloric acid (25 ml) and extracted with methylene chloride (2 x 50 ml). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*, chromatographed over silica gel, eluted with 20% ethyl acetate/hexanes, to afford 3-benzyl-4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid methyl ester (440 mg, 67%). IR (KBr) 1736 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.78 (dm, *J* = 13.5 Hz, 1H), 2.02-2.17 (m, 2H), 2.39 (dm, *J* = 13.5 Hz, 1H), 3.19-3.23 (m, 2H), 3.37-3.45 (td, *J* = 11.9, 2.4 Hz, 2H), 3.77-3.85 (m, 1H), 3.84 (s, 3H), 3.88-3.98 (m, 2H), 4.07-4.17 (m, 2H), 6.83-6.90 (m, 4H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.08-7.15 (m, 3H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H); FABMS (M^+ +H): 515.

EXAMPLE 32

Preparation of Compounds of Formula Ix

Preparation of Ix where n is 2, Y is hydroxy, R^1 and R^2 when taken together with the carbon to which they are attached are Tetrahydropyan-4-yl, R^3 is hydrogen, and R^4 is Benzyl, and R^5 is 4-(4-Chlorophenoxy)phenyl

To a solution of 3-benzyl-4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid methyl ester (410 mg, 0.80 mmol) in *N,N*-dimethylformamide (4 ml) was added lithium iodide (1.06 g, 7.96 mmol), followed by sodium cyanide (78 mg, 1.59 mmol). The mixture was heated to 120°C for 8 hours, cooled to room temperature, the *N,N*-dimethylformamide solvent removed by heating under reduced pressure, and the residue partitioned between ethyl acetate (150 ml) and saturated aqueous sodium bisulfite (50 ml). The ethyl acetate layer was dried over magnesium sulfate, concentrated *in vacuo*, purified by preparative chromatography (20 x 40-1000 um plates), eluted with 8% methanol/methylene chloride) to afford 317 mg (80%) of 3-benzyl-4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-carboxylic acid ^{1}HNMR (*N,N*-dimethylformamide contaminant, $CDCl_3$) δ 1.74 (dm, J = 13.5 Hz, 1H), 2.05-2.18 (m, 2H), 2.42 (dm, J = 13.5 Hz, 1H), 3.22-3.26 (m, 2H), 3.48-3.58 (m, 2H), 3.78-4.18 (m, 5H), 6.83-6.88 (m, 4H), 6.93 (d, J = 8.5 Hz, 2H), 7.08-7.13 (m, 3H), 7.36 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H); CIMS (NH_3, $M^+ + NH_4+$): 518.

EXAMPLE 33

Preparation of Compounds of Formula I

Preparation of I where n is 2, R^2 is -NR^6R^7, in which R^6 and R^7 are both Methyl, and R^5 is 4-phenoxyphenyl

To a solution of (*R*)-2-amino-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (1.6 g) in *N,N*-dimethylformamide (5 ml) was added potassium carbonate (0.5 g) and methyl iodide (550 µl). After stirring for 2.5 hours, the mixture was partitioned between ethyl acetate and water, and after the organic layer was dried over magnesium sulfate, solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 50% ethyl acetate/hexane to give (*R*)-*N*-*tert*-butoxy-2-dimethylamino-3-(4-phenoxyphenylsulfonyl)-propionamide (0.6 g).

This compound, (*R*)-*N*-*tert*-butoxy-2-dimethylamino-3-(4-phenoxyphenylsulfonyl)-propionamide, was dissolved in 1,2-dichloroethane (50 ml), cooled to -30°C and bubbled for 15-20 minutes with hydrochloric acid gas in a pressure tube. The flask was then sealed and the mixture stirred overnight. After cooling the tube was cautiously vented and its contents evaporated, to yield a gum, which upon trituration with 2:1 hexane/ethyl acetate gave a white powder, (*R*)-2-dimethylamino-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide hydrochloride (0.43 g), m.p. 65-70°C.

EXAMPLE 34

Preparation of Compounds of Formula I

Preparation of I where n is 2, R^2 is -NR^6R^7, in which R^6 is Hydrogen and R^7 is Dimethylaminosulfonyl, and R^5 is 4-phenoxyphenyl

To a solution of (*R*)-2-amino-*N*-*tert*-butoxy-3-(4-phenoxyphenylsulfonyl)-propionamide (1.5 g) in methylene chloride (20 ml) and pyridine (1.2 ml) was added dimethylsulfamoyl chloride (1 ml), and the mixture stirred overnight at room temperature. The mixture was partitioned between methylene chloride and water, and after the organic layer was dried over magnesium sulfate, solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-45% ethyl acetate/hexane, to give (*R*)-*N*-*tert*-butoxy-2-dimethylaminosulfonamido-3-(4-phenoxyphenylsulfonyl)-propionamide (1.6 g).

This compound, (*R*)-*N*-*tert*-butoxy-2-dimethylaminosulfonamido-3-(4-phenoxyphenylsulfonyl)-propionamide, was dissolved in trifluoroacetic acid (30 ml) and the mixture stirred overnight at room temperature. The trifluoroacetic acid was removed under reduced pressure, and the residue chromatographed on silica gel, eluting with 10% methanol/methylene chloride, to give (*R*)-2-dimethylaminosulfonamido-3-(4-phenoxyphenylsulfonyl)-*N*-hydroxypropionamide hydrochloride (550 mg). ^{1}H NMR (d6-DMSO) 7.90 (d,2H), 7.47 (d,2H), 7.25 (t,1H), 7.13 (m,4H), 3.95 (m,1H), 3.55 (m,2H), 2.6 (s,6H).

EXAMPLE 35

Example of Preparation of Compounds of Formula I on a Large Scale

Preparation of I where n is 2, R^1 and R^2 when taken together with the Carbon to which they are attached represent Tetrahydropyran, R^3 and R^4 are Hydrogen, and R^5 is 4-(4-Chlorophenoxy)phenyl

1. Preparation of a Compound of Formula (7a)

To a mixture of *N,N*-dimethylformamide (56 Kg) and diethyl malonate (22 Kg) was added a 21% solution of sodium ethoxide in ethanol (45 Kg), followed by 2-chloroethyl ether (19 Kg). The mixture was heated to 85°C, causing ethanol to distil from the mixture. The temperature was raised to 120°C until all the ethanol formed was removed (3 hours), and then the mixture was allowed to cool to 25°C. The mixture was then rewarmed to 120°C and a further 45 Kg of a 21% solution of sodium ethoxide in ethanol added at such a rate as to cause the ethanol formed to distil off. When the distillation was complete, the mixture was cooled to 100°C, and after it was determined that the reaction was complete then cooled to 25°C. The mixture was partitioned between toluene (80 Kg) and water (216 Kg) and solvent removed from the organic layer by distillation. The product was used in the next step with no further purification.

2. Preparation of a Compound of Formula (8a) where R^1 and R^2 when taken together with the Carbon Atom to which they are attached represent Tetrahydropyran

A solution of diethyl tetrahydro-4H-pyran-4,4-dicarboxylate, the compound of Formula (7a), (12 Kg) in toluene (104 Kg) was cooled to between -30°C to -35°C, and diisobutylaluminum hydride (69 Kg) was added at such a rate so as to maintain a reaction temperature of -25°C. After the addition was complete, the temperature was raised to 15°C over 3 hours, and the reaction stirred until all starting material was consumed. The mixture was then recooled to -15°C and allowed to stand overnight. The product was partitioned between ethyl acetate (54 Kg), ethanol (48 Kg), and saturated sodium sulfate solution (60 litres), and the mixture stirred overnight at 25°C. The precipitated salts were filtered off, washed with tetrahydrofuran, and the filtrate washed with brine and separated. The organic layer was dried over magnesium sulfate and solvent removed under reduced pressure, to give ethyl 4-hydroxymethyltetrahydropyran-4-carboxylate (3.8 Kg), the compound of Formula (8a).

3. Preparation of a Compound of Formula (9a) where R^1 and R^2 when taken together with the Carbon Atom to which they are attached represent Tetrahydropyran

To a solution of lithium hydroxide monohydrate (4.46 Kg) in methanol (44 litres) and water (11 Kg) was added ethyl 4-hydroxymethyl-tetrahydropyran-4-carboxylate (8.0 Kg). The mixture was refluxed for 30 minutes, then solvent removed under reduced pressure. The mixture was cooled to 20°C, methyl *tert*-butyl ether (14.8 Kg) added, stirred for 10 minutes, and allowed to settle. The top organic layer was separated. This was repeated twice more, then the remaining mixture cooled to -10°C, and a solution of 31% hydrochloric acid (13 Kg) in water (3 Kg) added, maintaining the temperature below 5°C. The mixture was extracted several times with tetrahydrofuran, and the combined organic phases dried over magnesium sulfate. Approximately 90% of the tetrahydrofuran was removed, and the remaining solution added to a mixture of hexane (64.5 Kg) and methyl *tert*-butylether (23.7 Kg) with stirring. The precipitated solid material was filtered off and dried under reduced pressure at 60°C, to give 4-hydroxymethyl-tetrahydropyran-4-carboxylic acid (3.7 Kg), the compound of Formula (9a).

4. Preparation of a Compound of Formula Ia where R^1 and R^2 when taken together with the Carbon Atom to which they are attached represent Tetrahydropyran

To a mixture of 4-hydroxymethyl-tetrahydropyran-4-carboxylic acid (3.84 Kg), 4-dimethylaminopyridine (0.6 Kg) in dichloromethane (32 litres) was added triethylamine (4.88 Kg). The mixture was cooled to -20°C, and a solution of benzenesulfonyl chloride (4.66 Kg) in dichloromethane (5 litres) was added over a period of 35 minutes, maintaining the temperature below -10°C. The mixture was stirred at -10°C for 30 minutes, then 3N hydrochloric acid (10 litres) and water (10 litres) were added with stirring, then the layers allowed to separate. The organic layer was separated, the aqueous layer washed with dichloromethane (16 litres), the combined organics washed with aqueous 5% sodium bicarbonate solution (12 litres), then with water (12 litres), and solvent removed under reduced pressure, to give 2,7-dioxaspiro[3,5]nonane-1-one, a compound of Formula (10a)

To a mixture of 60% sodium hydride (0.92 Kg) in tetrahydrofran (26 litres) at 0°C was added a solution of 4-(4-chlorophenoxy)thiophenol (4.37 Kg) in tetrahydrofuran (15 litres), maintaining the temperature below 10°C. The mixture was allowed to warm to room temperature for 30 minutes, then recooled to 0°C. The concentrated solution of 2,7-dioxas-

piro[3,5]nonane-1-one obtained above was then added slowly to this mixture, maintaining the temperature below 10°C. The mixture was allowed to warm to room temperature, and stirred for 30 minutes. The mixture was then treated with 3N hydrochloric acid (16 litres) and dichloromethane (30 litres). The organic layer was separated and the aqueous layer extracted twice with dichloromethane (20 litres). The combined organics were washed with water (20 litres), filtered, and 100 litres of solvent removed under atmospheric pressure. To the remaining reaction product was added acetonitrile (60 litres) and after a further 60 litres of solvent were removed by distillation, acetonitrile (40 litres) was added and the total volume of the remainder reduced to 30 litres by distillation. This mixture was then heated to mild reflux (80°C), and then slowly cooled to 0°C. The product was filtered off, washed with hexane, and dried to about 60°C under reduced pressure, to yield 4-[4-(4-chlorophenoxy)phenylthiomethyl]tetrahydropyran-4-carboxylic acid (5.61 Kg).

5. Preparation of a Compound of Formula Iba where R^1 and R^2 when taken together with the Carbon Atom to which they are attached represent Tetrahydropyran

A solution of 4-[4-(4-chlorophenoxy)phenylthiomethyl]tetrahydropyran-4-carboxylic acid (5.5 Kg) and *N,N*-dimethylformamide (27 ml) in dichloromethane (27.5 litres) was cooled to 5°C, and oxalyl chloride (1.4 litres) added slowly with stirring. After addition was complete, the mixture was allowed to warm to room temperature and stirred for 2 hours, thus forming a compound of Formula (12). The solution was then recooled to 10°C, and a mixture of 50% aqueous hydroxylamine (5.4 litres), *tert*-butanol (12.1 litres) and tetrahydrofuran (30.5 litres) was added slowly, maintaining the temperature below 21°C. The mixture was then allowed to warm to room temperature until the reaction was complete. The solvent was then evaporated under reduced pressure until 90% had been removed, at which point acetonitrile (42.5 litres) was added and the remaining dichloromethane removed by distillation under reduced pressure. The remaining solution was heated under reflux, and water (126 Kg) added at such a rate so as to maintain reflux. The solution was then cooled to 5°C for 12 hours, and the solid thus obtained filtered off. This product was washed with water and dried under vacuum at 50°C to yield 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) (5.06 Kg), a compound of Formula Iba.

6. Preparation of a Compound of Formula Id where R^1 and R^2 when taken together with the Carbon Atom to which they are attached represent Tetrahydropyran

To a solution of 4-[4-(4-chlorophenoxy)phenylthiomethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) (5.06 Kg) in tetrahydrofuran (28 litres) and methanol (112 litres) at 15°C was added a solution of OXONE (14.23 Kg) in water (72 litres) with stirring, ensuring that the temperature did not exceed 16°C. After the addition was complete, the temperature was raised to 20°C and the mixture stirred for 3 hours, then poured into a cold mixture (5°C) of toluene (60 litres) and ethyl acetate (98 litres) with stirring. The resultant mixture was filtered, the organic and aqueous layers thus obtained separated, and the aqueous layer washed with a mixture of ethyl acetate (25 litres) and toluene (10 litres). This wash was repeated twice more. The combined extracts and organic layer was washed twice with water (25 litres), and solvent removed under reduced pressure to a volume of 30 litres. The solution was cooled to 5°C, and the solid filtered off, washed with ethyl acetate/water and dried under vacuum at 50°C, to yield 4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide) (4.3 Kg).

7. Similarly other Compounds of Formula I may be prepared.

EXAMPLE 36

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, *e.g.*, *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide:

A.	
Ingredients	% wt./wt.
Compound of Formula I	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage.

B.	
Ingredients% wt./wt.	
Compound of Formula I	20.0%
Magnesium stearate	0.9%
Starch	8.6%
Lactose	79.6%
PVP (polyvinylpyrrolidine)	0.9%

The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid. The formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tablet machine.

C.	
Ingredients	
Compound of Formula I	0.1 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g
Polysorbate 80	1.0 g
Water	q.s. 100 ml

The compound of Formula I is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 ml of the solution which is filtered and bottled.

D.	
Ingredients	% wt./wt.
Compound of Formula I	20.0%
Peanut Oil	78.0%
Span 60	2.0%

The above ingredients are melted, mixed and filled into soft elastic capsules.

EXAMPLE 37

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, *e.g.*, *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide:

Ingredients	
Compound of Formula I	0.02 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g
Polysorbate 80	1.0 g
0.9% Saline solution	q.s. 100 ml

The compound of Formula I is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 ml of the I.V. solution which is filtered through a 0.2 μ membrane filter and packaged under sterile conditions.

EXAMPLE 38

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, *e.g., N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide:

Ingredients	% wt./wt.
Compound of Formula I	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

EXAMPLE 39

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, *e.g., N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide

Ingredients	% wt./wt.
Micronized compound of Formula I	1.0%
Micronized lactose	99.0%

The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump.

EXAMPLE 40

This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, *e.g., N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide:

Ingredients	% wt./wt.
Compound of Formula I	0.005%
Water	89.995%
Ethanol	10.000%

The compound of Formula I is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

EXAMPLE 41

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, *e.g.*, *N*-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl)]-acetamide:

Ingredients	% wt./wt.
Compound of Formula I	0.10%
Propellant 11/12	98.90%
Oleic acid	1.00%

The compound of Formula I is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

EXAMPLE 42

In Vitro Assay

42A. Isolation of MMPs for Assays

The catalytic domain of human collagenase-1 was expressed as a fusion protein with ubiquitin in *E. Coli* (Gehring, E.R. *et at., J. Biol. Chem.*, **270**, 22507, (1995)). After purification of the fusion protein, the fibroblast collagenase-1 catalytic domain was released by treatment with 1mM of aminophenylmercuric acetate (APMA) for 1 hour at 37°C and purified by zinc chelate chromatography.

Human collagenase-2 and gelatinase B were isolated in active form from buffy coats (Mookhtiar, K.A. *et at., Biochemistry*, **29**, 10620, (1990)).

The propeptide and catalytic domain portion of human collagenase-3 was expressed in *E. Coli* as an *N*-terminal fusion protein with ubiquitin. After purification, the catalytic domain was obtained by treatment with 1 mM APMA for 1 hour at 37°C, and purified by zinc chelate chromatography.

Rat collagenase-3 was purified in active form from the culture media of uterine smooth muscle cells (Roswit, W.T. *et al., Arch. Biochem. Biophys.*, **225**, 285-295 (1983)).

The catalytic and fibronectin-like portion of human progelatinase A was expressed as a fusion protein with ubiquitin in *E. Coli.* Assays were carried out on autolytically activated material. Rat progelatinase A was purified from the culture media of interleukin-1 stimulated keratinocytes and activated by treatment with 1 mM APMA for 1 hour at 37°C, and subsequently dialyzed to remove excess APMA.

Human prostromelysin-1 was purified from the culture medium of synovial fibroblasts by affinity chromatography using an immobilized monoclonal antibody. The zymogen was activated by treatment with trypsin (1.5 μg/ml) for 1 hour at 23°C to give a mixture of 45 and 28 kD species. The catalytic domain of human stromelysin was prepared by expression and purification of prostromelysin-1 from *E. Coli* and activated with 1 mM APMA for 1 hour at 37°C, followed by dialysis. Rat prostromelysin-1 was expressed in Chinese Hampster Ovary cells and purified from the culture media. It was activated by 1 mM APMA for 1 hour at 37°C, followed by dialysis.

Human promatrilysin was expressed and purified from Chinese Hampster Ovary cells (Barnett, *J. et al., Prot.*

Expres. Pur., **5**, 27, (1994)). The zymogen was activated by treatment with 1 mM APMA for 1 hour at 37°C, and purified by zinc chelate chromatography.

Compounds of Formula I exhibited the ability to inhibit the collagenases when tested in this assay.

42B. In Vitro Assay Procedure

Assays were performed in assay buffer (50 mM Tricine pH 7.5, 200 mM sodium chloride, 10 mM calcium chloride, 0.005% Brij-35) containing 2.5% methyl sulfoxide (DMSO) once the substrate and inhibitor were diluted into it. Stock solutions of inhibitors were prepared in 100% DMSO. Stock solutions of the substrate were prepared in 100% DMSO at a concentration of 2 mM.

The assay method was based on the hydrolysis of MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH_2 (Bachem, Inc.) at 37°C (Knight, C.G. *et al., FEBS,* **296**, 263-266 (1992)). The fluorescence changes were monitored with a Perkin-Elmer LS-50B fluorimeter using an excitation wavelength of 328 nm and an emission wavelength of 393 nm. The substrate concentration used in the assays was 10 μmole. The inhibitor was diluted into the assays from a solution in 100% DMSO, and controls substituted an equal volume of DMSO so that the final DMSO concentration from inhibitor and substrate dilutions in all assays was 2.5%. The inhibition results are expressed as the inhibitor concentration that produced 50% inhibition (IC_{50}) of the activity in the control (non-inhibited) reaction.

EXAMPLE 43

In Vitro Assay

This assay determines the ability of the compounds of Formula I to inhibit the degradation of the collagen matrix (as judged by release of hydroxyproline), and proteoglycan (as judged by the release of ^{35}S-labelled glycosaminoglycans) from cartilage explants.

Small cartilage explants (3 mm diameter) were prepared from freshly sacrificed bovine knee joints and labeled with $^{35}SO_4$. ^{35}S-labelled glycosaminoglycans (GAG's) and collagen fragments are released into the culture medium in response to the addition of rhIL-1-alpha, which induces the expression of chondrocyte matrix metalloproteases (MMP's), including stromelysin and collagenase. The percent inhibition of hydroxyproline and GAG's released was corrected for spontaneous release in the absence of rhIL-1-alpha.

Compounds of Formula I, when tested in this assay, displayed the ability to inhibit the release of both collagen fragments and ^{35}S-labelled GAG's from cartilage explants.

EXAMPLE 44

In Vivo Assay

The cartilage plug implantation assay measures the destruction of the collagen matrix of a cartilage plug implanted in a rat (Bishop, J. *et al., J. Pharm. Tox. Methods,* **30**, 19, (1993)).

Previously frozen bovine nasal cartilage plugs weighing approximately 20 mg were embedded in polyvinyl sponges impregnated with *Mycobacterium tuberculosis* and implanted subcutaneously in female Lewis rats. Dosing was begun 9 days after implantation and the plugs were harvested about one week later. The plugs were weighed, hydrolyzed, and the hydroxyproline content measured. Efficaciousness was determined by the comparison of the compound-treated groups with vehicle treated controls.

The compounds of Formula I exhibited the ability to inhibit the degradation of the cartilage plugs in this assay.

EXAMPLE 45

In Vivo Assay Procedure

45A. Determination of TNF Production Following LPS Stimulation

Female Balb/c mice, 6-8 weeks old (Jackson Labs or Harlan) were used. For each treatment group, 6-8 mice were used. Mice were injected I.P. with LPS (Sigma, 13129, 10-20 μg/mouse) after treatment with a compound of Formula I. The compound of Formula I or vehicle was administered subcutaneously (S.C.) once, 30-60 minutes prior to LPS challenge. Control animals received CMC vehicle alone or CMC + 2-5% DMSO. Animals were bled 1.5 hours after LPS injection under anesthesia with metofane from the retro-orbital plexus, using a Pasteur pipette. Blood was collected in a microtainer serum separator tube (Becton Dickinson #5960). The sera were separated and either tested the next day or they were kept at -20°C until ready to test for TNF-α.

45B. ELISA Assay for Murine TNF-α

The Endogen (EM-TNFA kit) mouse tumor necrosis factor alpha (mTNF-α) kit is an *in vitro* enzyme-linked immunosorbent assay for the quantitative measurement of mouse TNF-α (ordering code: EM-TNFA; Endogen, 30 Commerce Way, Woburn, MA 01801-1059, USA). Standards (lyophilized recombinant *E. coli*-derived mouse TNF-a) or serum samples (50 µl each) were added in duplicate to each well of the precoated anti-mTNF-α plate. Biotinylated antibody (50 µl) was added, the plates were incubated for 2-3 hours at room temperature. The wells were washed five times with wash buffer and 100 µl of diluted strepavidin HRP were added to each well and then were incubated at room temperature for 30 minutes. After washing (5X), 100 µl premixed TMB substrate solution were added to each well and plates were developed at room temperature in the dark for 30 minutes. The reaction was stopped by adding 100 µl of the stop solution. Absorbance at 450-575 nm was measured in a plate reader (ThermoMax, Molecular Devices). Results are calculated at pg/ml TNF-α by comparison to the standard curve, using Immunofit Beckman software. They are expressed as mean pg/ml of TNF-α, and as percentage of inhibition compared to controls (animals injected with LPS alone), considered 100% of TNF-α: production.

The compounds of Formula I, when tested in this assay, exhibited the ability to inhibit TNF-α production.

EXAMPLE 46

TNF Conjugate Immunoassay

Human Monomac 6 cells were cultured at 37°C in RPMI 1640 medium supplemented with 10% fetal calf serum to a density of 1 X 10^5 cells/mL. All subsequent incubations were performed at 37°C. 230 µl of these cells were placed in each well of a 96-well tissue culture plate and the cells incubated for 15 minutes. 10 µl of desired concentration of compounds of Formula I in the above mentioned medium were added to the appropriate wells and incubated for an additional 15 minutes. To each well was added 10 µl of an LPS/PMA mixture which brings the final concentration of LPS to 10 ng/mL and the final PMA concentration to 30 ng/mL. The cells were then incubated for 2 hours after which the plate was centrifuged and the medium removed and analyzed for TNF content. The analysis was performed using an R & D Systems TNF Quantikine Immunoassay and following the manufacturer's protocol (R & D. Systems, 614 Mckinley Place N.E., Minneapolis, MN 55413, USA; Catalog No. DTA50). The IC_{50} was calculated from the percent inhibition of TNF released into the medium.

The compounds of Formula I, when tested in this assay, exhibited the ability to inhibit TNF production.

EXAMPLE 47

TNFR Shedding Immunoassay

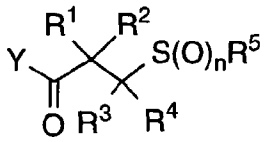
Human Monomac 6 cells are cultured to a density of 1 X 10^6 cells/mL at 37°C in RPMI 1640 medium supplemented with 10% fetal calf serum. All subsequent incubations are performed at 37°C. 230 µl of these cells are placed in each well of a 96-well tissue culture plate and the cells are incubated for 15 minutes. 10 µl of desired concentration of compounds of Formula I in the above mentioned medium are added to the appropriate wells and incubated for an additional 15 minutes. To each well is added 10 µl of PMA at a final concentration of 30 ng/mL. The cells are then incubated for 16 hours after which the plate is centrifuged and the medium is removed and analyzed for TNF receptor content. The analysis is performed using the R & D Systems TNF receptor Quantikine Immunoassay following the manufacturer's protocol. Measurements of each TNF receptor (receptor I and receptor II) are performed in this way. The IC_{50} is calculated from the percent inhibition of TNF released into the medium.

The compounds of Formula I, when tested in this assay, exhibited the ability to selectively inhibit TNF production.

While the present invention has been described with respect to specific embodiments thereof, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

1. A compound of the formula:



I

wherein:

n is 0, 1 or 2;
Y is hydroxy or XONH-, where X is hydrogen or lower alkyl;
R^1 is hydrogen or lower alkyl;
R^2 is hydrogen, lower alkyl, heteroalkyl, aryl, aralkyl, arylheteroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heteroarylheteroalkyl, heterocyclo, heterocylo-lower alkyl, heterocyclo-lower heteroalkyl or $-NR^6R^7$, wherein:

R^6 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl, aryl, heteroaryl and heteroaralkyl;
R^7 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)R^8$, $-C(O)NR^8R^9$, $-SO_2NR^8R^9$, $-SO_2R^{10}$, aryloxycarbonyl, or alkoxycarbonyl; or
R^6 and R^7 together with the nitrogen atom to which they are attached represent a heterocyclo group; wherein

R^8 and R^9 are independently hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or heteroalkyl; and
R^{10} is lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroalkyl or heterocyclo; or

R^1 and R^2 together with the carbon atom to which they are attached represent a cycloalkyl or heterocyclo group;
R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroalkyl or lower alkoxy;
R^4 is hydrogen, lower alkyl, cycloalkyl or cycloalkylalkyl; or
R^2 and R^3 together with the carbons to which they are attached represent a cycloalkyl or heterocyclo group; or
R^3 and R^4 together with the carbon to which they are attached represent a cycloalkyl or heterocyclo group; and
R^5 is lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

or a pharmaceutically acceptable salt or ester thereof.

2. The compound of Claim 1, wherein R^2 is $-NR^6R^7$.

3. The compound of Claim 1, wherein n is 2 and Y is XONH- in which X is hydrogen.

4. The compound of Claim 3, wherein R^1 is hydrogen and R^5 is aryl or heteroaryl.

5. The compound of Claim 4, wherein R^2 is hydrogen and R^3 is aralkyl and R^4 is hydrogen.

6. The compound of Claim 5, wherein R^3 is benzyl and R^5 is optionally substituted phenyl or naphthyl.

7. The compound of Claim 6, wherein R^5 is phenyl, 4-methoxyphenyl, 1-(4-methoxyphenyl)-2-phenylethene, phenylthiophenyl, phenoxyphenyl, or biphenyl.

8. The compound of Claim 7, wherein R^5 is 4-phenylthiophenyl, 4-phenoxyphenyl, or 4-biphenyl.

9. The compound of Claim 4, wherein R^3 and R^4 together with the carbon to which they are attached form a cycloalkyl group.

10. The compound of Claim 9, wherein R^5 is 4-methoxyphenyl or 4-phenoxyphenyl and the cycloalkyl group is cyclopentyl, cyclohexyl, or 4-methylcyclohexyl.

11. The compound of Claim 4, wherein R^3 and R^4 together with the carbon to which they are attached form a heterocyclo group.

12. The compound of Claim 11, wherein the heterocyclo group is optionally substituted piperidine or tetrahydropyranyl.

13. The compound of Claim 12, wherein the heterocyclo group is piperidin-4-yl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

14. The compound of Claim 12, wherein the heterocyclo group is 1-methylpiperidin-4-yl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

15. The compound of Claim 12, wherein the heterocyclo group is 1-(cyclopropylmethyl)piperidin-4-yl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

16. The compound of Claim 12, wherein the heterocyclo group is tetrahydropyran-4-yl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

17. The compound of Claim 3, wherein R^2 and R^3 together with the carbons to which they are attached form a cycloalkyl group and R^5 is aryl.

18. The compound of Claim 17, wherein the cycloalkyl group is cyclopentyl or cyclohexyl, R^4 is hydrogen, and R^5 is 4-methoxyphenyl.

19. The compound of Claim 3, wherein R^2 is $-NR^6R^7$, R^1, R^3 and R^4 are hydrogen, and R^5 is aryl.

20. The compound of Claim 19, wherein R^5 is 4-phenoxyphenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

21. The compound of Claim 3, wherein R^1 and R^2 together with the carbon to which they are attached form a heterocyclo group.

22. The compound of Claim 21, wherein R^3 and R^4 are both hydrogen and the heterocyclo group is optionally substituted piperidine or tetrahydropyranyl.

23. The compound of Claim 22, wherein the heterocyclo group is piperidin-4-yl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

24. The compound of Claim 22, wherein the heterocyclo group is tetrahydropyran-4-yl and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, 4-(4-fluorophenoxy)phenyl, 4-(thiophen-2-yl)phenoxyphenyl, 4-(thiophen-3-yl)phenoxyphenyl, 4-(2-pyridyloxy)phenyl, 4-(5-chloro-2-pyridyloxy)phenyl.

25. The compound of Claim 3, wherein R^1 and R^2 are both alkyl, R^3 and R^4 are hydrogen, and R^5 is 4-phenoxyphenyl, 4-(4-bromophenoxy)phenyl, 4-(4-chlorophenoxy)phenyl, or 4-(4-fluorophenoxy)phenyl.

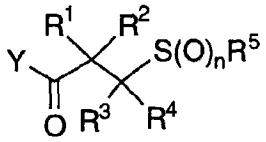
26. A compound of the group comprising

N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-tetrahydropyran-4-yl]-acetamide,
2-{4-[4-(4-chlorophenoxy)phenylsulfonyl]tetrahydropyran-4-yl}-*N*-hydroxyacetamide,
2-{4-[4-(4-fluorophenoxy)phenylsulfonyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide,
N-hydroxy-2-[4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide,
2-{4-[4-(4-chlorophenoxy)-phenylsulfonyl]piperidin-4-yl}-*N*-hydroxyacetamide,
2-{4-[4-(4-fluorophenoxy)-phenylsulfonyl]-piperidin-4-yl}-*N*-hydroxyacetamide,
N-hydroxy-2-[1-methyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-acetamide,
2-[1-cyclopropylmethyl-4-(4-phenoxyphenylsulfonyl)-piperidin-4-yl]-*N*-hydroxyacetamide,
2-{ 1-cyclopropylmethyl-4-[4-(4-chlorophenoxy)-phenylsulfonyl]piperidin-4-yl}-*N*-hydroxyacetamide,
2-{1-cyclopropylmethyl-4-[4-(4-fluorophenoxy)-phenylsulfonyl]piperidin-4-yl}-*N*-hydroxyacetamide
2-{4-[4-(4-fluorophenoxy)-phenylsulflnyl]-tetrahydropyran-4-yl}-*N*-hydroxyacetamide,
(*R*)-2-(CBZ-valinamido)-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide,
(*R*)-*N*-hydroxy-2-valinamido-3-(4-phenoxyphenylsulfonyl)propionamide,

(*R*)-2-dimethylamino-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)propionamide,
(*R*)-2-dimethylaminosulfonamido-*N*-hydroxy-3-(4-phenoxyphenylsulfonyl)-propionamide,
2-[4-[-(4-fluorophenoxy)-phenylthio]-tetrahydropyran-4-yl}-N-hydroxyacetamide,
4-[4-(4-chlorophenoxy)-phenylsulfonylmethyl]-tetrahydropyran-4-(*N*-hydroxycarboxamide),
4-[4-(4-thiophen-2-yl)phenoxyphenyl-sulfonylmethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide),
3-[4-(4-chlorophenoxy)-phenylsulfonyl]-2,2-dimethyl-N-hydroxypropionamide,
4-[4-(4-(thiophen-3-yl)-phenoxy)phenylsulfonylmethyl]tetrahydropyran-4-(*N*-hydroxycarboxamide)

and pharmaceutically acceptable salts thereof.

27. A process for preparing a compound of the Formula:

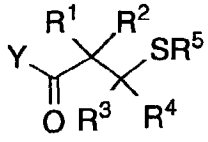


I

wherein:

n	is 1 or 2;
Y	is hydroxy or XONH-, where X is hydrogen or lower alkyl;
R^1	is hydrogen or lower alkyl;
R^2	is hydrogen, lower alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, or heterocyclo; or
R^1 and R^2	together with the carbon atom to which they are attached represent a cycloalkyl or heterocyclo group;
R^3	is hydrogen, lower alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, or lower alkoxy;
R^4	is hydrogen or lower alkyl; or
R^2 and R^3	together with the carbons to which they are attached represent a cycloalkyl or heterocyclo group; or
R^3 and R^4	together with the carbon to which they are attached represent a cycloalkyl or heterocyclo group; and
R^5	is lower alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

comprising contacting a compound of the Formula:



wherein R^1, R^2, R^3, R^4 and R^5 are as defined before,
with an oxidizing agent.

28. A pharmaceutical composition comprising a pharmaceutically acceptable non-toxic excipient and a therapeutically effective amount of a compound according to any one of claims 1-26.

29. Compounds according to any one of claims 1-26 for use as a therapeutically active substance.

30. Compounds according to any one of claims 1-16 for use in the treatment of a disease-state which is alleviated by treatment with a matrix metalloprotease inhibitor, especially wherein the disease state is rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, aberrant angiogenesis, multiple sclerosis, tumor metastasis, or corneal ulceration.

31. Compounds according to any one of claims 1-26 for use in the treatment of a disease state which is mediated by tumor necrosis factor, especially wherein the disease state is inflammation, hemorrhage, graft versus host reaction or an autoimmune disease.

32. The use of a compound according to any one of claims 1-26 in the treatment of of a disease-state which is alleviated by treatment with a matrix metalloprotease inhibitor, especially wherein the disease state is rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, aberrant angiogenesis, multiple sclerosis, tumor metastasis, or corneal ulceration.

33. The use of a compound according to any one of claims 1-26 in the treatment of a disease state which is mediated by tumor necrosis factor, especially wherein the disease state is inflammation, hemorrhage, graft versus host reaction or an autoimmune disease.

34. The use of a compound according to any one of claims 1-26 in the preparation of a medicament for the treatment of a disease-state which is alleviated by treatment with a matrix metalloprotease inhibitor, especially wherein the disease state is rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, aberrant angiogenesis, multiple sclerosis, tumor metastasis, or corneal ulceration or wherein the disease-state is mediated by tumor necrosis factor, especially wherein the disease state is inflammation, hemorrhage, graft versus host reaction or an autoimmune disease.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,P	WO 96 15096 A (BAYER AG ;KLUENDER HAROLD CLINTON EUGENE (US); BENZ GUENTER H H H) 23 May 1996 * examples 196-198 * ---	1	C07D309/08 C07D211/54 C07D213/64 C07D401/06 C07D407/12 C07D413/12 C07D405/12 A61K31/35 A61K31/445
X	WO 90 05719 A (BRITISH BIO TECHNOLOGY) 31 May 1990 * examples1-3,8-18,20-24 * ---	1,28,29	
X	WO 95 09841 A (BRITISH BIOTECH PHARM ;CRIMMIN MICHAEL JOHN (GB); BECKETT PAUL RAY) 13 April 1995 * examples 1-7 * ---	1,28,29	
X,P	WO 96 06074 A (BRITISH BIOTECH PHARM ;BECKETT RAYMOND PAUL (GB); MILLER ANDREW (G) 29 February 1996 * example 13 * ---	1	
X	WO 93 20047 A (BRITISH BIO-TECHNOLOGY LTD) * examples 1-9,11-14 * --- -/--	1,28,29	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K
C07C
C25D

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
BERLIN	10 April 1997	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	US 4 394 520 A (KALOPISSIS GREGOIRE) 19 July 1983 * examples 4,5,18; table I * ---	1	
X	US 4 268 516 A (LOMBARDINO JOSEPH G ET AL) 19 May 1981 * example 4 * ---	1	
X	FR 1 580 899 A (BRISTOL-MYERS COMPANY) 12 September 1969 * examples 4-7 * ---	1,28,29	
X	FR 2 355 095 A (M & T CHEMICALS INC) 13 January 1978 * compound page 21 * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CAS REGISTRY HANDBOOK: , AMERICAN CHEMICAL SOCIETY , 1965-1971 XP002028919 * RN: 331-89-5;331-90-8;331-93-1;405-23-2;780-95-0;5463-52-5;5464-62-0;5445-04-5;5445-05-6;5460-58-2;6803-08-3;6534-37-8;21056-72-4 * ---	1	
X	TETRAHEDRON, vol. 49, no. 4, 1993, OXFORD GB, pages 939-946, XP002028918 S.E. CLAYTON ET AL.: * compound (8), page 940 * --- -/--	1	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X,P	CHEMICAL ABSTRACTS, vol. 125, no. 13, 23 September 1996 Columbus, Ohio, US; abstract no. 167779x, XP002028920 * abstract * & JP 08 127 581 A (SANKYO CO.) 21 May 1996 * CAS Registry (STN database), RN: 13739-36-1 * ---	1	
X	CHEMICAL ABSTRACTS, vol. 93, no. 19, 10 November 1980 Columbus, Ohio, US; abstract no. 186144y, XP002028921 * abstract * & JP 55 027 116 A (HOKKO CHEMICAL INDUSTRY CO.) * CAS Registry (STN database), RN:13739-35-0 * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 77, no. 13, 25 September 1972 Columbus, Ohio, US; abstract no. 88024j, XP002028922 * abstract * & TETRAHEDRON LETTERS, vol. 19, 1972, OXFORD GB, pages 1937-1940, R.H. RYNBRANDT ET AL.: * CAS Registry (STN database), RN: 36603-44-8;36603-37-9;36603-36-8;35930-65-5 * --- -/--	1	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 76, no. 21, 22 May 1972 Columbus, Ohio, US; abstract no. 126719d, XP002028923 * abstract * & AUST. J. CHEM., vol. 25, no. 3, 1972, pages 647-653, G.F. KATEKAR ET AL.: * compounds I * ---	1	
X	CHEMICAL ABSTRACTS, vol. 74, no. 3, 18 January 1971 Columbus, Ohio, US; abstract no. 13116v, XP002028924 * abstract * & HELV. CHIM. ACTA, vol. 53, no. 7, 1970, pages 1813-1827, P. DOSTERT ET AL.: * CAS Registry (STN database), RN: 30013-62-8;30037-18-4;30037-19-5 * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 69, no. 19, 4 November 1968 Columbus, Ohio, US; abstract no. 76817s, XP002028925 * abstract * & ANN. UNIV. MARIAE CURIE-SKLODOWSKA, SECT. AA. 1966, vol. 21, 1967, pages 49-64, M. JANCZEWSKI ET AL.: * CAS Registry (STN database), RN: 20025-59-6 * --- -/--	1	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 69, no. 19, 4 November 1968 Columbus, Ohio, US; abstract no. 75267a, XP002028926 * abstract * & BIOCHEM. J. , vol. 109, no. 1, 1968, pages 143-147, B. GILLHAM ET AL.: * CAS Registry (STN database), RN: 21462-48-6 * ---	1	
X	CHEMICAL ABSTRACTS, vol. 67, no. 15, 9 October 1967 Columbus, Ohio, US; abstract no. 73477d, XP002028927 * abstract * & J. INDIAN CHEM. SOC., vol. 43, no. 7, 1966, pages 521-525, A.B. SEN ET AL.: * CAS Registry (STN database), RN: 15773-92-9 * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 67, no. 9, 28 August 1967 Columbus, Ohio, US; abstract no. 43615e, XP002028928 * abstract * & BULL. SOC. CHIM. FR., vol. 11, 1966, pages 3674-3682, P. CAGNIANT ET AL.: * CAS Registry (STN database), RN: 6112-45-9 * ---	1	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 66, no. 11, 13 March 1967 Columbus, Ohio, US; abstract no. 46292n, XP002028929 * abstract * & BOLL. SCI. FAC. CHIM. IND. BOLOGNA, vol. 24, no. 2-3, 1966, pages 75-91, I. DEGANI ET AL.: * CAS Registry (STN database), RN:13735-04-1;13735-02-9 * ---	1	
Y	WO 95 33731 A (HOFFMANN LA ROCHE ;BROADHURST MICHAEL JOHN (GB); BROWN PAUL ANTHON) 14 December 1995 * the whole document * ---	1,28,29	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
Y	WO 95 29892 A (DU PONT MERCK PHARMA) 9 November 1995 * the whole document * ---	1,28,29	
Y	EP 0 606 046 A (CIBA GEIGY AG) 13 July 1994 * the whole document * ---	1,28,29	
Y	CHEMICAL ABSTRACTS, vol. 93, no. 7, 18 August 1980 Columbus, Ohio, US; abstract no. 61046m, XP002028930 * abstract * & ARZNEIM.-FORSCH., vol. 30, no. 4A, 1980, pages 695-702, R.G. CHILD ET AL.: ---	1,28,29	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 96 11 9780

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y,D	J. ENZYME INHIBITION, vol. 2, 1987, pages 1-22, XP000197047 W.H. JOHNSON ET AL.: * compound (V), page 7; table III, page 9 * -----	1,28,29	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

EP 96119780 - C -

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extend that is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely:
Claims searched incompletely: all
Claims not searched:

Reason for the limitation of the search:

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of all claims.
Reason:

The huge number of theoretically conceivable compounds resulting from the combinations of all the substituent definitions claimed in claim 1 prevents the search from being carried out comprehensively. Additionally such an uncertainty on the claimed scope may introduce contradictions and render unity questionable. Guided by the description, the search has been limited to the scope (IPC sub-divisions) which is illustrated by the compounds explicitely mentioned in the application. It is noted nevertheless that many individual compounds fall within the searched scope and therefore it is not possible to cite all of the documents found which are prejudicial to the novelty of the claimed invention. The documents cited as X-documents in the present search report are only a selection thereof.

EPO Form Supplementary Sheet C (1996)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 818 442 A2

(12) EUROPEAN PATENT APPLICATION

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(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **12.07.1996 US 21652 P**

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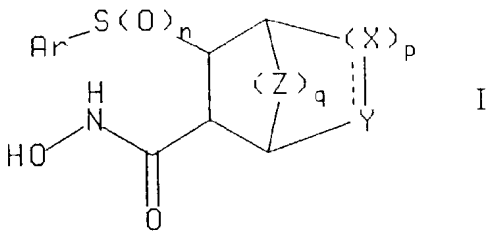
(54) Cyclic sulphone derivatives as inhibitors of metalloproteinases and of the production of tumour necrosis factor

(57) A compound of the formula



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wherein n, p, q, X, Y, Z and Ar are as defined herein, useful in the treatment of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis or other diseases characterized by matrix metalloprotenase activity, as well as AIDS, sepsis, septic shock or other diseases involving the production of TNF.

EP 0 818 442 A2

Description

Background of the Invention

The present invention relates to cyclic sulfone derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases involving the production of TNF.

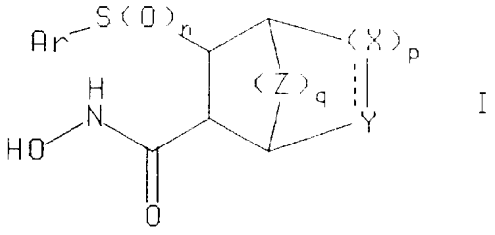
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and autoimmune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al . Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



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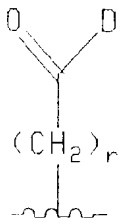
or a pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond:

n is 0, 1 or 2.

p is 0 or 1;

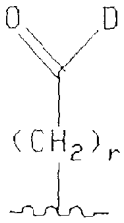
q is 0, 1 or 2;

X, Y and Z are each independently CR^1R^2 wherein R^1 and R^2 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted by $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_6\text{-}C_{10})$arylsulfinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, amino, $(C_1\text{-}C_6)$alkylamino or $((C_1\text{-}C_6)\text{alkyl})_2$amino; $(C_2\text{-}C_6)$alkenyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkenyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkynyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_1\text{-}C_6)$alkyl (difluoromethylene), (C_1C_3)alkyl(difluoromethylene) $(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy. $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $R^3(C_1\text{-}C_6)$alkyl wherein R^3 is $(C_1\text{-}C_6)$acylpiperazino, $(C_6\text{-}C_{10})$arylpiperazino, $(C_5\text{-}C_9)$heteroarylpiperazino, $(C_1\text{-}C_6)$alkylpiperazino, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperazino, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$arylpiperidyl, $(C_6\text{-}C_9)$heteroarylpiperidyl, $(C_1\text{-}C_6)$alkylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_9)$heteroarylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$acylpiperidyl, or a group of the formula



wherein r is 0 to 6;

D is hydroxy, (C_1-C_6)alkoxy or NR^4R^5 wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl or (C_3-C_6)cycloalkyl; piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_6)heteroarylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, R^6(C_2-C_6)alkyl, (C_1-C_9)alkyl(CHR^6)(C_1-C_6)alkyl wherein R^6 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R^7(C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^7)(C_1-C_6)alkyl wherein R^7 is piperidyl or (C_1-C_6)alkylpiperidyl; and $CH(R^8)COR^9$ wherein R^8 is hydrogen, (C_1-C_6)alkyl, (C_5-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_5-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino (C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^{10}R^{11}NCO$(C_1-C_6)alkyl or $R^{10}OCO$ (C_1-C_6)alkyl wherein R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^9 is $R^{12}O$ or $R^{12}R^{13}N$ wherein R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and Ar is (C_6-C_{10})aryl or (C_5-C_9)heteroaryl, each of which may be optionally substituted by (C_6-C_{10})aryl, (C_5-C_9)heteroaryl,(C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_5-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl or (C_5-C_9)heteroaryl(C_2-C_6)alkynyl optionally substituted by (C_1-C_6)alkyl, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio (C_1-C_6)alkoxy, trifluoromethyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino,(C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(hydroxymethylene), piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_5-C_9) heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino,(C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino or R^3alkyl wherein R^3 is defined as above; halo, hydroxy, (C_1-C_6)alkyl or (C_1-C_6)alkoxy wherein the alkyl or alkoxy groups may be optionally substituted by (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_6)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(hydroxymethylene), piperazinyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_8)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6) alkyl)$_2$amino; (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_6-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10}) aryl(C_2-C_6)alkynyl. (C_5-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, R^3(C_1-C_6)alkyl or R^3(C_1-C_6)alkoxy wherein $R^3$is(C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl, (C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_5-C_9)heteroarylpiperidyl(C_1-C_6)alkyl, (C_1-C_6)acylpiperidyl, or a group of the formula



wherein r and D are as defined above;

with the proviso that when q is 1 and X and Y are both CR^1R^2 wherein one of either R^1 or R^2 must be hydrogen, p must be 1;
with the proviso that when q is 0, the compound of formula I is not bicyclic: and
with the proviso that when the broken line of formula I represents a double bond, R^2 does not exist.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes alkyl-O groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluoro, chloro, cyano, nitro, trifluoromethyl, $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryloxy, trifluoromethoxy, difluoromethoxy and $(C_1\text{-}C_6)$alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl. isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents independently selected from the group consisting of fluoro, chloro, trifluoromethyl, $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryloxy, trifluoromethoxy, difluoromethoxy and $(C_1\text{-}C_6)$alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes acyl-O groups wherein "acyl" is defined above.

Preferred compounds of formula I include those wherein q is 0 or 2.

Other preferred compounds of formula I include those wherein q is 0 or 1

Other preferred compounds of formula I include those wherein n is 2

Other preferred compounds of formula I include those wherein X and Y are both CR^1R^2 wherein R^1 and R^2 are hydrogen.

Other preferred compounds of formula I include those wherein Ar is methoxyphenyl, phenoxyphenyl, benzoxyphenyl or halophenyl

More preferred compounds of formula I include those wherein q is 0, p is 1. m is 2, X and Y are CR^1R^2 are hydrogen and Ar is methoxyphenyl, phenoxyphenyl or benzoxyphenyl.

More preferred compounds of formula I include those wherein q is 0, p is 0, m is 2, X and Y are CR^1R^2 are hydrogen and Ar is methoxyphenyl, phenoxyphenyl or benzoxyphenyl.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

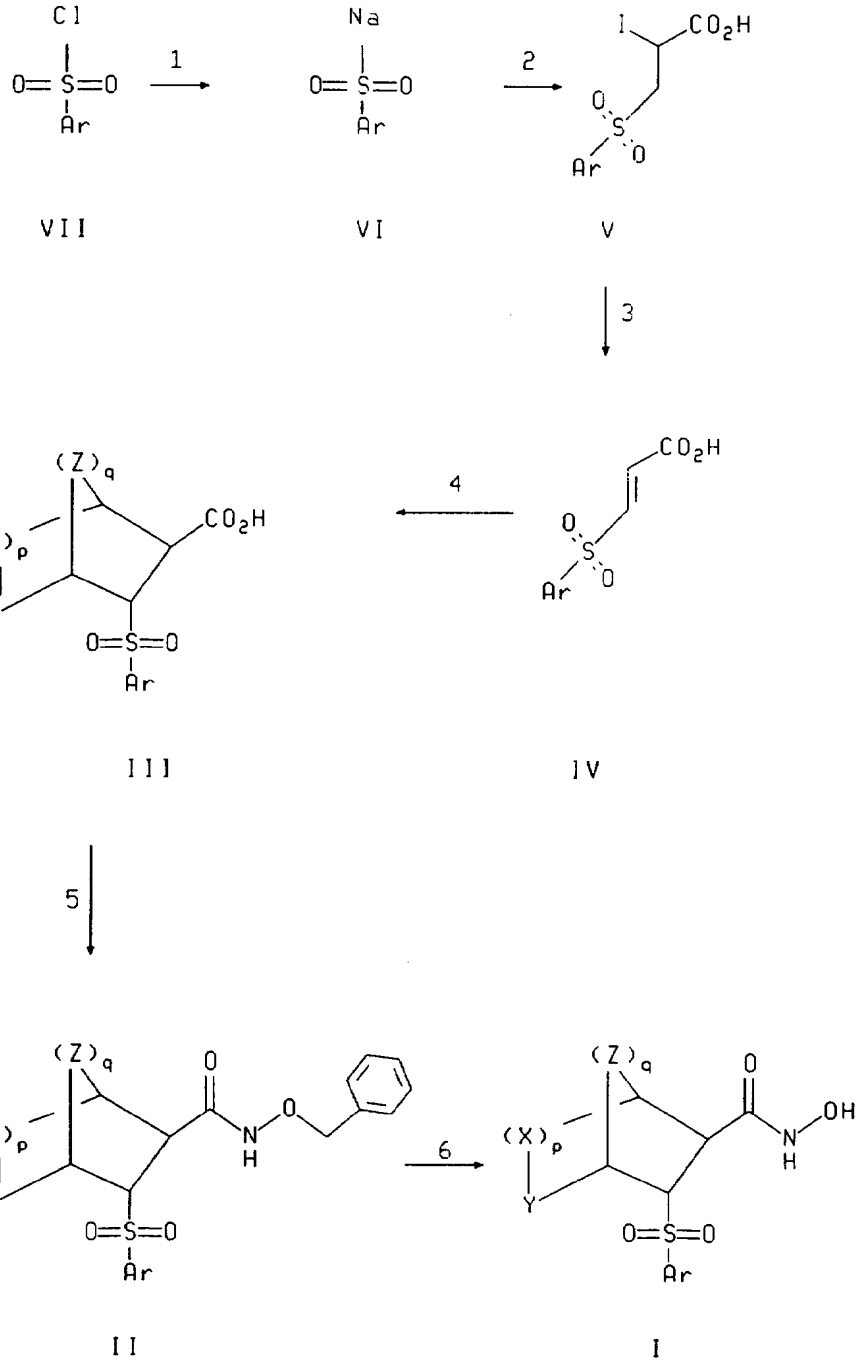
The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of

tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated p, q, X, Y, Z and Ar in the reaction Schemes and the discussion that follow are defined as above.

SCHEME 1

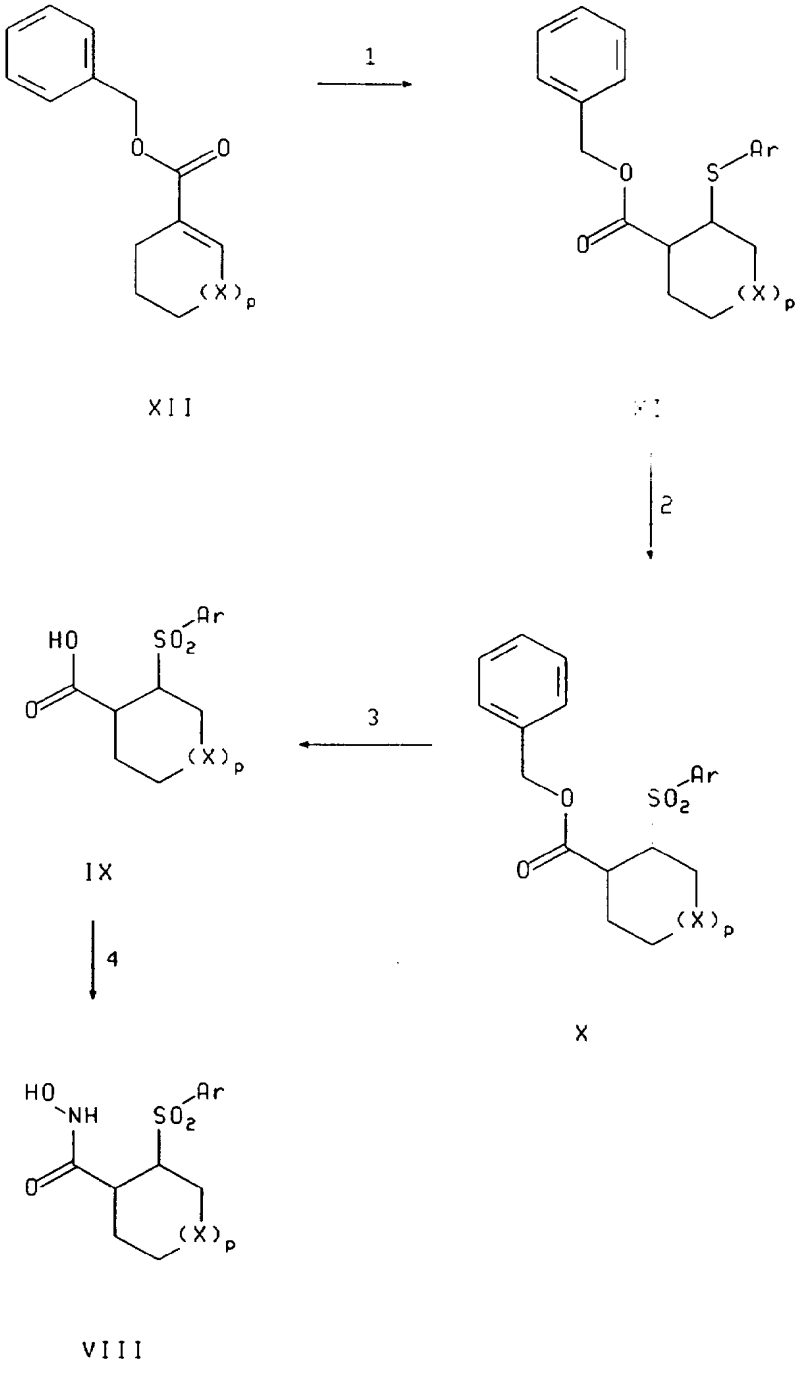


VII VI V

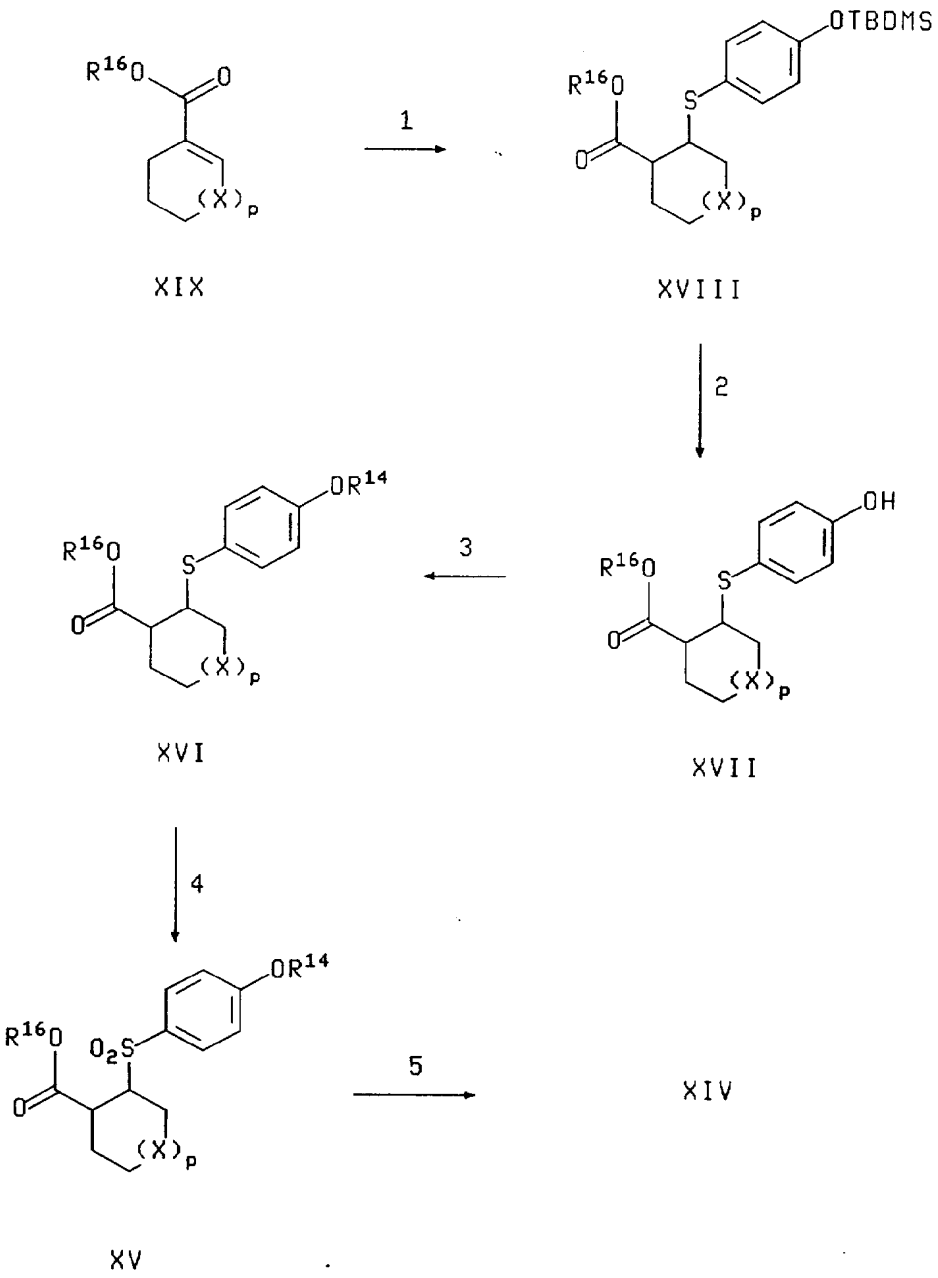
III IV

II I

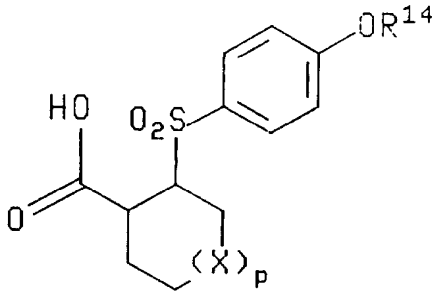
SCHEME 2



SCHEME 3

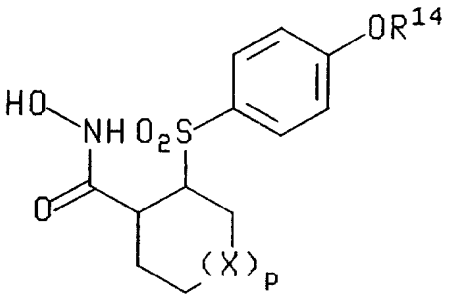


SCHEME 3 (Continued)



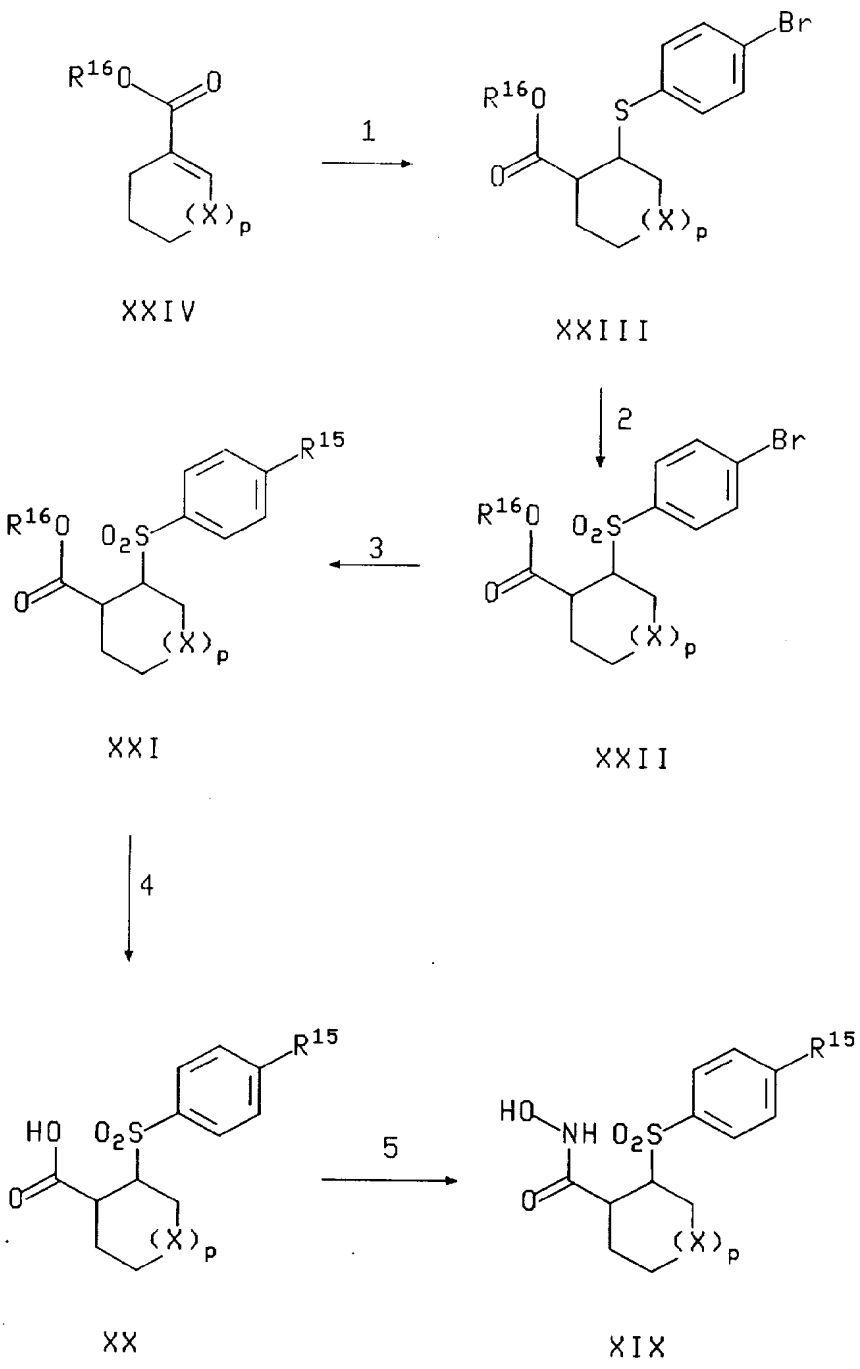
XIV

6

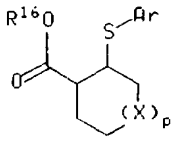


XIII

SCHEME 4

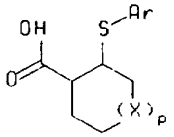


SCHEME 5



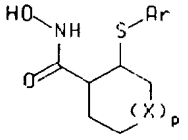
XXVIII

1



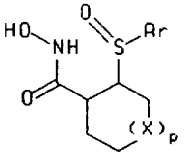
XXVII

2



XXVI

3



XXV

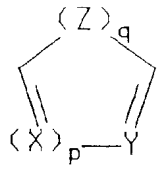
In reaction 1 of Scheme 1, the aryl sulfonyl chloride compound of formula **VII** is converted to the corresponding sodium aryl sulfinate compound of formula **VI** by reacting **VII** with sodium iodine in the presence of a polar aprotic solvent, such as acetone, under inert atmosphere. The reaction mixture is stirred, at room temperature. for a time period between about 12 hours to about 18 hours, preferably about 15 hours.

In reaction 2 of Scheme 1, the compound of formula **VI** is converted to the corresponding 2-iodo-3-(aryl) sulfonyl propionic acid compound of formula **V** by reacting **VI** with acrylic acid and iodine in the presence of a polar aprotic

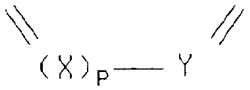
solvent, such as methylene chloride. The reaction mixture is stirred under inert atmosphere, at room temperature, for a time period between about 2.5 days to about 3.5 days, preferably about 3 days.

In reaction 3 of Scheme 1, the compound of formula **V** is converted to the corresponding (E)-3-(aryl)sulfonyl-prop-2-enoic acid compound of formula **IV** by treating **V** with a base, such as triethylamine, under inert atmosphere. The reaction is stirred, at room temperature, for a time period between about 10 hours to about 14 hours, preferably about 12 hours

In reaction 4 of Scheme 1, the compound of formula **IV** is converted to the corresponding carboxylic acid compound of formula **III** by heating **IV** with an excess amount of a compound of the formula



wherein q is 1 and p is 1, or an excess amount of the diene compound of the formula



wherein q is 0 and p is 1, to reflux in the presence of a polar aprotic solvent, such as toluene, for a time period between about 40 hours to about 56 hours, preferably about 48 hours.

In reaction 5 of Scheme 1, the compound of formula **III** is converted to the corresponding N-(benzyloxy)-carboxamide compound of formula **III** by reacting **II** with benzylhydroxylaminehydrochloride, dimethylaminopyride and dicyclohexylcarbodiimide in the presence of a polar aprotic solvent, such as methylene chloride, under inert atmosphere The reaction mixture is stirred, at room temperature, for a time period between about 15 hours to about 25 hours, preferably about 20 hours.

In reaction 6 of Scheme 1, the compound of formula **II** is converted to the corresponding hydroxamic acid compound of formula **I** by treating **II** with hydrogen in the presence of a catalyst, such as 5% palladium on barium sulfate, and a polar aprotic solvent, such as methanol. The reaction mixture is stirred for a time period between about 2 hours to about 4 hours, preferably about 3 hours.

In reaction 1 of Scheme 2, the cycloalkenecarboxylate compound of formula **XII**. wherein p is 0 or 1 and X is CH_2, is converted to the corresponding arylthiocycloalkanecarboxylate compound of formula **XI** by adding a solution of **XII** in a polar aprotic solvent, such as tetrahydrofuran, to a solution of an arylthio compound of the formula ArSH and a base, such as butyl lithium, in a polar aprotic solvent, such as tetrahydrofuran, under inert atmosphere, at a temperature between about -75°C to about -85°C, preferable about -78°C. The reaction mixture is allowed to warm to ambient temperature over a time period between about 10 hours to about 14 hours, preferably about 12 hours.

In reaction 2 of Scheme 2, the compound of formula **XI** is oxidized to the corresponding sulfone compound of formula **X** by treating **XI** with a suitable oxidant, such as a catalytic amount of osmium tetraoxide, and a reoxidant, such as N-methylmorpholine oxide, in a polar protic solvent, such as isopropanol. The reaction is carried out in a polar protic solvent, such as isopropanol, for a time period between about 4 hours to about 24 hours, preferably about 12 hours.

In reaction 3 of Scheme 2, the compound of formula **X** is converted to the corresponding carboxylic acid compound of formula **IX** by cleaving the ester moiety of **X** by either hydrolysis using a suitable base, such as sodium hydroxide, in a polar solvent, such as aqueous tetrahydrofuran, or hydrogenolysis using hydrogen in the presence of a polar solvent, such as methanol, and a catalyst, such as 10% palladium on carbon, under a pressure between about 40 psi to about 60 psi, preferably about 50 psi. The reaction is stirred for a time period between about 2 hours to about 12 hours, preferably about 8 hours.

In reaction 4 of Scheme 2, the carboxylic acid compound of formula **IX** is converted to the corresponding hydroxamic acid compound of formula **VIII** by treating **II** with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively. a protected derivative of hydroxylamine or its salt form, where the hydroxyl group

is protected as a tert-butyl, benzyl or allyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorphosphate and a base. such as N-methylmorpholine Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. N,O-bis (4-methoxybenzyl)hydroxylamine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

In reaction 1 of Scheme 3, the compound of formula **XIX**, wherein p is 0 or 1, X is CH_2 and R^{16} is a protecting group, such as benzyl, is converted to corresponding compound of formula **XVIII**, by reacting **XIX** with a 4-tert-butyldimethylsilylarylthio compound, according to the procedure described above in reaction 1 of Scheme 2.

In reaction 2 of Scheme 3, the compound of formula **XVIII** is converted to the corresponding compound of formula **XVII** by the addition of aqueous hydrofluoric acid to a solution of **XVIII** in a polar aprotic solvent, such as acetonitrile. The reaction mixture is stirred, at room temperature, for a time period between about 2 hours to about 5 hours, preferably about 4 hours.

In reaction 3 of Scheme 3, the compound of formula **XVII** is converted to the corresponding compound of formula **XVI**, wherein R^{14} is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted by $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperazinyl,$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_6\text{-}C_{10})$arylsulfinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, amino, $(C_1\text{-}C_6)$alkylamino or $((C_1\text{-}C_6)\text{alkyl})_2$amino; or R^3alkyl wherein R^3 is defined as above, by stirring **XVII** and suitable primary or secondary alcohol in a polar aprotic solvent. such as tetrahydrofuran, under inert atmosphere. A azidodicarboxylate, such as diethylazidodicarboxylate, and a trialkyl ortriarylphosphine, such as triphenylphosphine, are added and the resulting reaction mixture is stirred for a time period between about 10 hours to about 14 hours, preferably about 12 hours.

In reaction 4 of Scheme 3, the compound of formula **XVI** is oxidized to the corresponding sulfone compound of formula **XV** according to the procedure described above in reaction 2 of Scheme 2.

In reaction 5 of Scheme 3, the compound of formula **XV** is converted to the carboxylic acid compound of formula **XIV** according to the procedure described in reaction 3 of Scheme 2.

In reaction 6 of Scheme 3, the compound of formula **XVI** is converted to the corresponding hydroxamic acid compound of formula **XIII** according to the procedure described above in reaction 4 of Scheme 2.

In reaction 1 of Scheme 4, the compound of formula **XXIV**, wherein p is 0 or 1, X is CH_2 and R^{16} is a protecting group, such as benzyl, is converted to the corresponding compound of formula **XXIII** by reacting **XXIV** with a 4-halothiophenol, such as 4-bromothiophenol, according to the procedure described above in reaction 1 of Scheme 2.

In reaction 2 of Scheme 4, the compound of formula **XXIII** is converted to the corresponding compound of formula **XXII** according to procedures described above in reacton 4 of Scheme 3.

In reaction 3 of Scheme 4, the compound of formula **XXII** is converted to the corresponding compound of formula **XXI**, wherein R^{15} is hydrogen, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkenyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_9)$heteroaryl optionally substituted by $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino,$(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}(C_6)$alkyl(hydroxymethylene), piperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$acylamino,$(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$ alkylsulfinyl, $(C_6\text{-}C_{10})$arylsullinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsullonyl, amino, $(C_1\text{-}C_6)$alkylamino or $((C_1\text{-}C_6)$ alkyl$)_2$amino; or R^3alkyl wherein R^3 is defined as above. Coupling partners could be aryl or heteroaryl boronic acids, aryl or heteroaryl stannanes or vinyl compounds.

In reaction 4 of Scheme 4, the compound of formula **XXI** is converted to the corresponding compound of formula **XX** according to the procedure described above in reaction 3 of Scheme 2.

In reaction 5 of Scheme 4, the compound of formula **XX** is converted to the corresponding compound of formula **XIX** according to the procedure described above in reaction 4 of Scheme 2.

In reaction 1 of Scheme 5, the compound of formula **XXVIII**, wherein p is 0 or 1, X is CH_2 and R^{16} is a protecting group, such as benzyl, is converted to the corresponding compound of formula **XXVII** according to the procedure described above in reaction 3 of Scheme 2.

In reaction 2 of Scheme 5, the compound of formula **XXVII** is converted to the corresponding compound of formula **XXVI** according to the procedure described above in reaction 4 of Scheme 2.

In reaction 3 of Scheme 5, the thioether compound of formula **XXVI** is oxidized to the corresponding sulfoxide compound of formula **XXV** using a suitable oxidising agent, such as m-chloroperbenzoic acid, in a polar aprotic solvent, such as dichloromethane, at a temperature between about -10°C to about 10°C, preferably about 0°C, for a period of

time between about 30 minutes to about 4 hours, preferably about 2 hours.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium. magnesium, as well as ammonium slats, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data Data is plotted as inhibitor concentration vs % contro inhibitor fluorescence divided by fluorescence of collagenase alone × 100) IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147. 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-SCH[$CH_2CH(CH_3)_2$]CO-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 µl of a 10 mg/ml trypsin stock per 26 µg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 µl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 µl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 µg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 µl per well yielding at 1 mM final concentration

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 µL to the appropriate wells yields final concentrations of 3 µM, 0.3 µM, 0.003 µM, and 0.0003 µM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 µl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20µM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 µM, 3µM, 0.3 µM, and 0.03 µM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared asfor inhibition of human collagenase (MMP-1) and 50 µl is added to each well to give a final assay concentration of 10 µM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 µM, inhibitors are then assayed at final concentrations of 0.3 µM, 0.03 µM, 0.003 µM and 0.0003 µM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2×10^6/ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180µ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200µl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to humans for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor, a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any

event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically, e.g., when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The present invention is illustrated by the following examples, but is not limited to the details thereof.

EXAMPLE 1

N-Hydroxy-3-(4-phenoxy-benzenesulfonyl)-bicyclo[2.2.2]octane-2-carboxamide

A mixture of O-benzyl hydroxamate (0.17 grams; 0.36 mmol) and 5% palladium or barium sulfate (0.30 grams) in methanol (50 mL) was placed under an atmosphere of hydrogen (40 psi) and shaken vigorously for 3 hours. The reaction mixture was then filtered and concentrated in vacuo to provide a glassy solid (0.15g). Purification via flash chromatography (30:70:2.5:0.5 of ethyl acetate:hexanes:acetic acid:methanol) on silica gel produced the pure hydroxamic acid as an off-white foamy solid (96 mg; 60%). M.P. 89.9-91.8°C; ^{1}H NMR (250 MHz, D_4-MeOH) δ 7.80 (d, 2H, J=8.6 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.23 (t, 1H, J = 7.3 Hz), 7.11 (t, 4H, J = 9.1 Hz), 3.88 (d, 1H. J= 7.7 Hz), 2.84 (d, 1H, J = 7.2 Hz), 2.18 (br s, 2H), 1.80-1.40 (m. 4H); ^{13}C NMR (75 5 MHz, D_4-MeOH) δ 21.5, 25.9, 26.6, 27.4, 32.3, 42.4, 63.6, 118.8, 121.5, 126.2, 131.3, 132.0, 133.1, 156.6, 164.1, 171.8; IR (drifts): 3303-3230, 2943, 2870, 1665, 1582, 1488, 1247, 1143 cm^{-1}. HRMS: calculated for $C_{21}H_{24}NO_5$ 402.1375; Found 402.1352.

EXAMPLE 2

3-(4-phenoxy-benzenesulfonyl)-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid

A stirred solution of vinyl sulfone-carboxylate (0.34 grams; 1.1 mmol) and 1,3-cyclohexadiene (5-mL, excess) in dry toluene (10 mL) was heated to reflux (120°C) for 48 hours. The reaction was concentrated in vacuo to give a blue-green oil (0.73 grams) which was purified via flash chromatography (20% ethyl acetate, 2% acetic acid, 2% methanol in hexanes on silica gel) to give the bicyclic sulfone as a light yellow oil (0.24 grams; 56%). Major Diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85-7.74 (m, 2H), 7.44-7.37 (m, 2H), 7.22 (c, 1H), 7.10-7.01 (m, 4H), 6.30 (t, 1H, J = 6.9 Hz), 6.11 (t, 1H, J = 6.9 Hz), 3.13 (d, 1H, J = 4.9 Hz), 2.89 (dd, 1H, J = 5.8, 2.1 Hz), 2.63-2.57 (m, 2H), 1.90-1.16 (m, 4H). LRMS: 385 (M + 1), 402 (M + 18).

EXAMPLE 3

N-Hydroxy-2-(4-methoxybenzenesulfonyl)-cyclohexane-1-carboxamide

N-Butyl lithium (0.56ml of a 2.5M solution in hexanes) was added to a stirred solution of 4-methoxythiophenol (1.94 grams. 13.9 mmol) in tetrahydrofuran (40ml) at -78°C under a nitrogen atmosphere. After 1 hour a solution of benzyl

1-cyclohexene-1-carboxylate (6 grams, 27.8 mmol) in tetrahydrofuran (5 ml) was added by cannula and the reaction mixture was allowed to warm to room temperature over 12 hours. The reaction was quenched with saturated sodium chloride solution and diluted with ethyl acetate. The organic layer was separated, dried over sodium sulfate and concentrated. The crude mixture was purified by silica gel chromatography (elution with 98% hexane/2% ethyl acetate) to provide benzyl-2-(4-methoxybenzenothio)-1-cyclohexane-1-carboxylate.

Osmium tetroxide (1.85ml of a 2.5% solution in 2-methyl-2-propanol) was added to a stirred solution of benzyl-2-(4-methoxybenzenethio)-1-cyclohexane-1-carboxylate (3.3 grams, 9.27 mmol) and 4-methylmorpholine N-oxide (2.71 grams, 23.2 mmol) in aqueous acetone (40ml water/80ml acetone) at room temperature. After 2 hours the solvent was removed *in vacuo* and the residue was partitioned between dilute hydrochloric acid an dethyl acetate. The ethyl acetate layer was washed with brine, dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 90% hexane/10% ethyl acetate) to provide benzyl-2-(4-methoxybenzenesulfonyl)-1-cyclohexane-1-carboxylate.

Benzyl-2-(4-methoxybenzenesulfonyl)-1-cyclohexane-1-carboxylate(3.1grams, 8.0 mmol) was dissolved in 300ml ethyl alcohol. 10% Palladium on carbon (0.3 grams) was added and the reaction mixture was heated at 60°C under a pressure of 50psi hydrogen for 12 hours. The mixture was cooled, the catalyst removed by filtration and the solvent concentrated. The crude mixture was purified by silica gel chromatography (elution with 95% dichloromethane/5% methanol) to provide 2-(4-methoxybenzenethio)-1-cyclohexane-1-carboxylate.

1-Hydroxybenztriazole (0.49grams, 3.6mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.69 grams, 3.6 mmol) were added to a stirred solution of 2-(4-methoxybenzenesulfonl)-1-cyclohexane-1-carboxylate (0.9 grams, 3.0 mmol) in dimethylformamide (20ml) at room temperature. After 30 minutes hydroxylamine hydrochloride (0.83 grams, 12.0 mmol) and triethylamine (1.83 grams, 18.1 mmol) were added and the mixture was stirred for 12 hours The reaction mixture was diluted with ethyl acetate and washed with sodium bicarbonate solution. The organic layer was washed with 2M hydrochloric acid, then brine and dried (sodium sulfate) before concentrating. The product was purified by recrystailization (ethyl acetate/methanol) to give N-hydroxy-2-(4-methoxybenzenesulfonyl)-cyclohexane-1-carboxamide as a crystalline solid. The relative stereochemistry of the two substituents at the ring junction was shown to be *cis* by X-ray crystallography Mass spectrum (thermospray): m/Z 331.1 (MNH_4^+). ^1H NMR ($CDCl_3$, 400MHz, ppm) δ 9.00 (s, 1H), 7.80 (d, 2H), 7.05 (d, 1H), 3.90 (s,3H), 3.15 (dt, 1H), 3.10 (m, 1H), 2.20-1.85 (m, 4H), 1.80-1.20 (m, 6H). Analysis found: C,53,69; H, 6.15; N, 4 37 $C_{14}H_{19}NSO_6$ requires C,53.66; H, 6.11; N. 4.47.

EXAMPLE 4

N-Hydroxy-2-(4-(2-N-phthalimido)ethoxy-benzenesulfonyl)-cyclohexane-1-carboxamide

N-Butyl lithium (1.5ml a 2.5M solution in hexanes) was added to a stirred solution of 4-t-butyldimethylsilyloxthiophenol11 4.8 grams, 61.7 mmol) in tetrahydrofuran (300ml) at -78°C under a nitrogen atmosphere. After 1 hour a solution of benzyl 1-cyclohexene-1-carboxylate (8 grams, 37 mmol) in tetrahydrofuran (15 ml) was added by cannula and the reaction mixture was allowed to warm to room temperature over 12 hours. The reaction was quenched with saturated sodium chloride solution and diluted with ethyl acetate. The organic layer was separated, dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 98% hexane/2% ethyl acetate) to provide benzyl-2-(4-t-butyldimethylsilyloxybenzenethio)-1-cyclohexane-1-carboxylate.

Hydrofluoric acid (5ml of a 40% aqueous solution) was added to a stirred solutionobenzyl-2-(4-t-butyldimethylsilyloxybenzenothio)-1-cyclohexane-1-carboxylate (5 grams, 11.3 mmol) in acetonitrole (50ml) at room temperature. After 12 hours the reaction mixture was poured into aqueous ammonium chloride and extracted with dichloromethane. The organics were dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 97% dichloromethane/3% methanol) to provide benzyl-2-(4-hydroxybenzenethio)-1-cyclohexane-1-carboxylate.

Benzyl-2-(4-hydroxybenzenethio)-1-cyclohexane-1-carboxylate (1 gram, 2.92 mmol) and N-(2-hydroxyethyl) phthalimide (0.56 grams, 292 mmol) were dissolved in tetrahydrofuran (30ml) and stirred at 0°C under a nitrogen atmosphere. Triphenylphosphine (0.84 grams, 3.22 mmol) and diethylazidodicarboxylate (0.61 grams, 3.51 mmol) were then added and the solution was stirred for 12 hours at 50°C. The mixture was concentrated and the residue partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 99% dichloromethane/1% methanol) to provide benzyl-2-(4-(2-N-phthalimido)ethoxybenzenethio)-1-cyclohexane-1-carboxylate.

Osmium tetroxide (0.38ml of a 2.5% solution in 2-methyl-2-propanol) was added toa stirred solutionofbenzyl-2-(4-2-N-phthalimido)ethoxy-benzenethio)-1-cyclohexane-1-carboxylate (0.98 grams, 1.91 mmol) and 4-methylmorpholine N-oxide (0.56 grams, 4.77 mmol) in aqueous acetone (7ml water/14ml acetone) at room temperature. After 12 hours the solvent was removed *in vacuo* and the residue was partitioned between dilute hydrochloric acid and ethyl

acetate. The ethyl acetate layer was washed with brine, dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 99% dichloromethane/1% methanol) to provide benzyl-2-(4-(2-N-phthalimido)ethoxy-benzenesulfonyl)-1-cyclohexane-1-carboxylate.

Benzyl-2-(4-(2-N-phthalimido)ethoxy-benzenesulfonyl)-1-cyclohexane-1-carboxylate (0.54 grams, 1.0 mmol) was dissolved in 60ml ethyl alcohol. 10% Paladium on carbon (60mg) was added and the reaction mixture was heated at 60°C under a pressure of 50psi hydrogen for 12 hours. The mixture was cooled, the catalyst removed by filtration and the solvent concentrated. The crude mixture was purified by silica gel chromatography (elution with 98% dichloromethane/2% methanol) to provide 2-(4-(2-N-phthalimido)ethoxy-benzenesulfonyl)-1-cyclohexane-1-carboxylate.

1-Hydroxybenztriazole (78 mg, 0.58 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.11 grams, 0.58 mmol) were added to a stirred solution of 2-(4-(2-N-phthalimido)ethoxy-benzenesulfonyl)-1-cyclohexane-1-carboxylate (0.22grams,0.48 mmol) in dimethylformamide (5ml) at room temperature. After 30 minutes hydroxylamine hydrochloride (0.13 grams, 1.92 mmol) and triethylamine (0.29 grams, 2.89 mmol) were added and the mixture was stirred for 12 hours. The reaction mixture was diluted with ethyl acetate and washed with sodium bicornate solution. The organic layer was washed with 2M hydrochloric acid, then brine and dried (sodium sulfate) before concentrating The product was purified by silica gel chromatography (elution with 98% dichloromethane/2% methanol) to provide N-hydroxy-2-(4-(2-N-phthalimido)ethoxy-benzenesulfonyl)-cyclohexane-1-carboxamide, Mass spectrum (thermospray): m/Z 473 (MH^+). ^1H NMR ($CDCl_3$, 400MHz, ppm) δ 7.90-7.80 (m, 4H), 7.75 (d, 2H), 7.10 (d, 2H), 4.40 (t, 2H), 4.10 (t, 2H), 2.80 (m, 1H), 2.40 (dt, 1H), 1.90-1.20 (m, 8H). Analysis found: C,57.85; H, 5.30; N, 5.94. $C_{23}H_{24}N_2SO_7$. H_2O requires C, 57.37; H, 5.23; N, 5.82.

The title compounds of Example 5-6 were prepared by a method analogous to that described in Example 4.

EXAMPLE 5

N-Hydroxy -2-4-(benzyloxy)benzenesulfonyl)-cyclohexane-1-carboxamide

Mass spectrum (thermospray): m/Z 407.1 (MNH_4^+). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.80 (d, 2H), 7.50-7.30 (m, 5H), 7.20 (d, 2H), 5.20 (d, 2H), 2.80 (m, 1H), 2.40 (dt, 1H), 1.90-1.30 (m,8H). Analysis found: C,59.90; H, 5.83; N, 3.08. $C_{20}H_{23}NSO_5$. $O.5H_2O$ requires C,60.28; H, 6.07; N, 3.52.

EXAMPLE 6

N-Hydroxy-2-4-(4-methoxyphenpropyloxy)benzenesulfonyl)-cyclohexane-1-carboxamide

Mass spectrum (thermospray): m/Z 449.2 (MH^+). ^1H NMR ($CDCl_3$, 400MHz, ppm) δ 9.30 (1H, br s), 7.75 (2H, d), 7.10 (d, 2H), 7.00 (d, 2H), 6.85 (d, 2H), 4.60 (d, 1H), 4.00 (t, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.10 (dt, 1H), 2.75 (t, 3H), 2.25 (d, 1H), 2.10 (m, 2H), 1.70-1.10 (m, 8H).

EXAMPLE 7

N-Hydroxy-2-4-2-methoxy-5-pyridyl)-benzenesulfonyl)-cyclohexane-1-carboxamide

N-Butyl lithium (0.92ml of a 2.5M solution in hexanes) was added to a stirred solution of 4-bromothiophenol (4.37 grams, 23 mmol) in tetrahydrofuran (30ml) at -78°C under a nitrogen atmosphere. After 1 hour a solution of benzyl 1-cyclohexene-1-carboxylate (5 grams, 23 mmol) in tetrahydrofuran (10ml) was added by cannula and the reaction mixture was allowed to warm to room temperature over 12 hours. The reaction was quenched with saturated sodium chloride solution and diluted with ethyl acetate. The organic layer was separated, dried (sodium sulfate) and concentrated The crude mixture was purified by silica gel chromatography (elution with 95% hexane/5% ethyl acetate) to provide benzyl-2-(4-bromobenzenethio)-1-cyclohexane-1-carboxylate.

Osmium tetroxide (1.53ml of a 2.5% solution in 2-methyl-2-propanol) was added toastirred solutionofbenzyl-2-(4-bromobenzenethio)-1-cyclohexane-1-carboxylate (3.1 grams, 7.65 mmol) and 4-methylmorpholine N-oxide (2.24 grams, 19 mmol) in aqueous acetone (15 ml water/30ml acetone) at room temperature. After 12 hours the solvent was removed in vacuo and the residue was partitioned between dilute hydrochloric acid and ethyl acetate. The ethyl acetate layer was washed with brine, dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with dichloromethane) to provide benzyl-2-(4-bromobenzenesulfonyl)-1-cyclohexane-1-carboxylate.

Tetrakis-(triphenylphoshine)palladium (65mg, 0.057 mmol) was added to a stirred solution of 2-methoxypyridyl-5-boronic acid (460mg, 2.4 mmol) and benzyl-2-(4-bromobenzenesulfonyl)-1-cyclohexane-1-carboxylate (712mg, 1.6 mmol) in a mixture of toluene (9 ml), ethanol (5ml) and saturated sodium bicarbonate solution (4 ml). The mixture was

refluxed for 3 hours after which time the organic solvent was removed by evaporation. The residue was extracted with ethyl acetate and the organics were washed with water and saturated sodium chloride solution. The organics were dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 99% dichloromethane/1% methanol) to provide benzyl-2-(4-(2-methoxy-5-pyridyl)-benzenesulfonyl)-1-cyclohexane-1-carboxylate.

Benzyl-2-(4-(2-methoxy-5-pyridyl)-benzenesulfonyl)-1-cyclohexane-1-carboxylate (230 mg, 0.49 mmol) was dissolved in 20ml ethanol. 10% Palladium on carbon (30 mg) was added and the reaction mixture was heated at 60°C under a pressure of 50psi hydrogen for 12 hours. The mixture was cooled, the catalyst removed by filtration and the solvent concentrated. The crude mixture was purified by silica gel chromatography (elution with 95% dichloromethane/5% methanol) to provide 2-(4-(5-(2-methoxypyridyl)benzenesulfonyl)-1-cyclohexane-1-carboxylate.

1-Hydroxybenztriazole (80 mg, 0.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (143 mg, 0.7 mmol) were added to a stirred solution of 2-(4-(2-methoxy-5-pyridyl)-benzenesulfonyl)-1-cyclohexane-1-carboxylate (200 mg, 0.5 mmol) in dichloromethane (8 ml) at room temperature. After 30 minutes tert-butyldimethylsilyhydroxylamine (157mg, 1 mmol) and 4-methylmorpholine (0,14ml, 1 mmol) were added and the mixture was stirred for 12 hours. The solvent was removed and the reaction mixture was stirred for 2 hours in methanol/water (10ml/4 ml). The reaction mixture was concentrated and the crude mixture was purified by silica gel chromatography (elution with 98% dichloromethane/2% methanol) to provide N-hydroxy-2-(4-(2-methoxy-5-pyridyl))benzenesulfonyl)-cyclohexane-1-carboxamide. Mass spectrum (thermospray): m/Z 391 (MH^+), 408 (MNH_4^+). ^1H NMR ($CDCl_3$, 400MHz, ppm) δ 8.40 (s, 1H), 7.90 (d, 2H), 7.80 (d, 1H), 7.65 (d, 2H), 6.80 (d, 1H), 4.00 (s, 3H), 3.20 (m. 1H), 3.05 (m, 1H), 2.30-1.20 (m, 8H).

EXAMPLE 8

N-Hydroxy-2-(4-bromobenzenesulfoxy)-cyclohexane-1-carboxamide

N-Butyl lithium (2.86 ml of a 2.5M solution in hexanes) was added to a stirred solution of 4-bromothiophenol (14.8 grams, 78.5 mmol) in (300ml) at -78°C under a nitrogen atmosphere. After 1 hour a solution of methyl 1-cyclohexene-1-carboxylate (10 grams, 71.4 mmol) in tetrahydrofuran (20 ml) was added by cannula and the reaction mixture was allowed to warm to room temperature over 12 hours. The reaction was quenched with saturated sodium chloride solution and diluted with ethyl acetate. The organic layer was separated, dried (sodium sulfate) and concentrated. The crude mixture was dissolved in dioxane (250 ml) and water (80ml) and 2M sodium hydroxide solution (100 ml) was added. The mixture was stirred for 12 hours and then the pH was adjusted to pH 1-3 with concentrated hydrochloric acid. The dioxane was removed by evaporation and the product was extracted into dichloromethane. The organic layer was dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 30% ethyl acetate/70% hexane) to provide 2-(4-bromobenzenethio)-1-cyclohexane-1-carboxylate (contaminated with cyclohexene-1-carboxylate).

1-Hydroxybenztriazole (1.9 grams, 14 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2.69 grams, 14 mmol) were added to a stirred solution of 2-(4-bromobenzenethio)-1-cyclohexane-1-carboxylate (3.69 grams, 11.6 mmol) in dimethylformamide (50ml) at room temperature. After 30 minutes hydroxylamine hydrochloride (3.25 grams, 47 mmol) and triethylamine (9.7ml, 70 mmol) were added and the mixture was stirred for 12 hours. The solvent was removed and the reaction mixture was extracted from water with ethyl acetate. The organics were concentrated and the crude mixture was purified by silica gel chromatograph (elution with 98% dichloromethane/2% methanol) to provide N-hydroxy-2-(4-bromobenzenethio)cyclohexane-1-carboxamide.

m-Chloroperbenzoic acid (273 mg, 0.8 mmol of 50% pure solid) was added to a stirred solution of N-hydroxy-2-(4-bromobenzenethio)-cyclohexane-1-carboxamide (290 mg, 0.88 mmol) in dichloromethane (5ml) at 0°C. After 2 hours the mixture was diluted with further dichloromethane and washed with brine. The organic layer was dried (sodium sulfate) and concentrated. The crude mixture was purified by silica gel chromatography (elution with 98% dichloromethane/2% methanol) to provide N-hydroxy-2-(4-bromobenzenesulfoxy)-cyclohexane-1-carboxamide. Mass spectrum (thermospray): m/Z 346 (MH^+). ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.50 (br s, 1H), 7.70 (d, 2H), 7.55 (d, 2H), 2.95 (m, 1H), 2.80 (m, 1H), 2.20-2.00 (m, 2H), 1.90-1.10 (m, 6H).

EXAMPLE 9

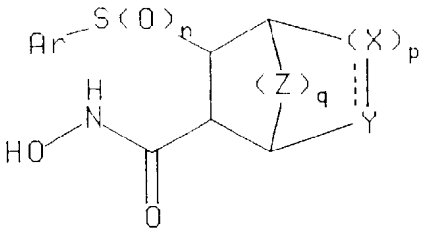
N-hydroxy-2-(4-methoxybenzenesulfoxy)-cyclohexane-1-carboxamide

The title compound of Example 9 was prepared by a method analogous to that described in Example 8.

Mass spectrum (thermospray): m/Z 298.0 (MH^+). ^1H NMR ($CDCl_3$, 400MHz, ppm) δ 7.60 (d, 2H), 7.10 (d, 2H), 3.90 (s, 3H), 3.00 (m, 1H), 2.90 (m, 1H), 2.25 (m, 1H). 2.10-1.40 (m, 7H).

Claims

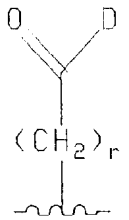
1. A compound of the formula



I

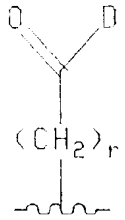
or a pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

n is 0, 1 or 2;
p is 0 or 1;
q is 0, 1 or 2;
X, Y and Z are each independently CR^1R^2 wherein R^2 and R^2 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted by $(C_1\text{-}C_6)$alkylamino. $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_6\text{-}C_{10})$arylsulfinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, amino, $(C_1\text{-}C_6)$alkylamino or $((C_1\text{-}C_6)\text{alkyl})_2$amino; $(C_2\text{-}C_6)$alkenyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkenyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkynyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_1\text{-}C_6)$alkyl (difluoromethylene), (C_1C_3)alkyl(difluoromethylene)$(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $R^3(C_1\text{-}C_6)$alkyl wherein R^3 is $(C_1\text{-}C_6)$acylpiperazino, $(C_6\text{-}C_{10})$arylpiperazino, $(C_5\text{-}C_9)$heteroarylpiperazino, $(C_1\text{-}C_6)$alkylpiperazino, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperazino, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$arylpipeiidyl, $(C_5\text{-}C_9)$heteroarylpiperidyl, $(C_1\text{-}C_6)$alkylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_9)$heteroarylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$acylpiperidyl, or a group of the formula



wherein r is 0 to 6:
D is hydroxy, $(C_1\text{-}C_6)$alkoxy or NR^4R^5 wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen. $(C_1\text{-}C_6)$alkyl optionally substituted by $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$arylpiperidyl, $(C_5\text{-}C_9)$heteroarylpiperidyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl or $(C_3\text{-}C_6)$cycloalkyl; piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$arylpiperidyl, $(C_5\text{-}C_9)$heteroarylpiperidyl, $(C_1\text{-}C_6)$acylpiperidyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cycloalkyl, $R^6(C_2\text{-}C_6)$alkyl, $(C_1\text{-}C_5)$alkyl$(CHR^6)(C_1\text{-}C_6)$alkyl wherein R^6 is hydroxy, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$alkoxy, piperazino, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$alkylthio, $(C_6\text{-}C_{10})$arylthio, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_6\text{-}C_{10})$arylsulfinyl, $(C_1\text{-}C_6)$alkylsulfoxyl, $(C_6\text{-}C_{10})$arylsulfoxyl, amino, $(C_1\text{-}C_6)$alkylamino, $((C_1\text{-}C_6)\text{alkyl})_2$amino, $(C_1\text{-}C_6)$acylpiperazino, $(C_1\text{-}C_6)$alkylpiperazino, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperazino, $(C_6\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; $R^7(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_5)$alkyl$(CHR^7)(C_1\text{-}C_6)$alkyl wherein R^7 is piperidyl or $(C_1\text{-}C_6)$alkylpiperidyl; and CH

$(R^8)COR^9$ wherein R^8 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylthio$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfinyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfinyl $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, amino $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $((C_1\text{-}C_6)$alkylamino$)_2(C_1\text{-}C_6)$alkyl, $R^{10}R^{11}NCO(C_1\text{-}C_6)$alkyl or $R^{10}OCO(C_1\text{-}C_6)$alkyl wherein R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl and $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl; and R^9 is $R^{12}O$ or $R^{12}R^{13}N$ wherein R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl and $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl; and Ar is $(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_9)$heteroaryl, each of which may be optionally substituted by $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl,$(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkenyl,$(C_5\text{-}C_9)$ heteroaryl$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkynyl or $(C_5\text{-}C_9)$heteroaryl$(C_7\text{-}C_6)$alkynyl optionally substituted by $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkyithio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy,$(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$ alkoxy, $(C_1\text{-}C_8)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_6\text{-}C_{10})$arylsulfinyl $(C_1\text{-}C_6)$ alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, amino, $(C_1\text{-}C_6)$alkylamino, $((C_1\text{-}C_6)$alkyl$)_2$amino or R^3alkyl wherein R^3 is defined as above; halo, hydroxy, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy wherein the alkyl or alkoxy groups may be optionally substituted by $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino. $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_3\text{-}C_6)$cydoalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl (hydroxymethylene), piperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxyl $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$ acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_6\text{-}C_{10})$arylsulfinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl, amino, $(C_1\text{-}C_6)$alkylamino or $((C_1\text{-}C_6)$alkyl$)_2$amino; $(C_2\text{-}C_6)$alkenyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$ alkenyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_6)$alkynyl, $(C_5\text{-}C_9)$heteroaryl$(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, $(C_1\text{-}C_6)$alkyl (difluoromethylene), $(C_1\text{-}C_3)$alkyl(difluoromethylene)$(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$arylamino, $(C_6\text{-}C_{10})$arylthio, $(C_6\text{-}C_{10})$aryloxy, $(C_5\text{-}C_9)$heteroarylamino, $(C_5\text{-}C_9)$heteroarylthio, $(C_5\text{-}C_9)$heteroaryloxy, $(C_3\text{-}C_6)$ cycloalkyl, $(C_1\text{-}C_6)$alkyl(hydroxymethylene), piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_1\text{-}C_6)$acylamino, $(C_1\text{-}C_6)$acylthio, $(C_1\text{-}C_6)$acyloxy, $R^3(C_1\text{-}C_6)$alkyl or $R^3(C_1\text{-}C_6)$alkoxy wherein R^3 is $(C_1\text{-}C_6)$acylpiperazino, $(C_6\text{-}C_{10})$arylpiperazino, $(C_5\text{-}C_9)$heteroarylpiperazino, $(C_1\text{-}C_6)$alkylpiperazino, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperazino. $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$arylpiperidyl, $(C_5\text{-}C_9)$heteroarylpiperidyl, $(C_1\text{-}C_6)$alkylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_9)$heteroarylpiperidyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$acylpiperidyl, or a group of the formula



wherein r and D are as defined above;
with the proviso that when q is 1 and X and Y are both CR^1R^2 wherein one of either R^1 or R^2 must be hydrogen, p must be 1;
with the proviso that when q is 0, the compound of formula I is not bicyclic; and
with the proviso that when the broken line of formula I represents a double bond, R^2 does not exist

2. A compound according to claim 1, wherein q is 0 or 2.

3. A compound according to claim 1, wherein q is 0 or 1.

4. A compound according to claim 1, wherein n is 2

5. A compound according to claim 1, wherein X and Y are both CR^1R^2 wherein R^1 and R^2 are hydrogen.

6. A compound according to claim 1, wherein Ar is methoxyphenyl, phenoxyphenyl, benzoxyphenyl or halophenyl.

7. A compound according to claim 1, wherein q is 0, p is 1, m is 2, X and Y are CR^1R^2 are hydrogen and Ar is methoxyphenyl, phenoxyphenyl or benzoxyphenyl.

8. A compound according to claim 1, wherein q is 0, p is 0, m is 2, X and Y are CR^1R^2 are hydrogen and Ar is methoxyphenyl, phenoxyphenyl or benzoxyphenyl.

9. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments and a pharmaceutically acceptable carrier

10. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

11. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal. including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

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(54) A latent mercaptan as a heat stabilizer

(57) Flexible, semi-rigid, and rigid vinyl chloride polymer compositions comprising a latent mercaptan-containing heat stabilizer are substantially free from the offensive odour typically associated with mercaptans and are protected during processing by the degradation products of the latent (i.e., blocked) mercaptan which include a free mercaptan. The free mercaptan thus released enhances the activity of metallic-based heat stabilizers such as zinc carboxylates and organotin carboxylates and mercaptides in the polymer composition. Other products of the degradation are believed to include carbocations of the blocking moiety which are stabilized by a molecular structure in which the electron deficiency is shared by several groups. The latent mercaptan is selected from a 2-S-(tetrahydropyranyl)-thioalkanol, a carboxylic acid ester thereof, a 2-S-(tetrahydropyranyl)-thioglycolic acid, and an ester thereof.

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Description

FIELD OF THE INVENTION

[0001] This invention relates to a heat stabilized halogen-containing polymer composition normally susceptible to heat-induced deterioration which comprises a halogen-containing polymer and the degradation products of a latent mercaptan present during processing of the composition at an elevated temperature, said products being formed during said processing and including a liberated mercaptan. The free mercaptan enhances the activity of metal-based heat stabilizers such as organotin carboxylates and mercaptides in the polymer composition. It particularly relates to the stabilization against heat of vinyl chloride polymer compositions and articles made thereof by a latent mercaptan selected from the group consisting of 2-S-(hydroxyalkylthio)tetrahydropyran, 5-S-(hydroxyalkylthio) tetrahydrofuran, and the carboxylic acid esters thereof in combination with very low levels of a metal-based heat stabilizer or certain Lewis acids. Said latent mercaptans are also referred to hereinafter as 2-S-(tetrahydropyranyl)-thioalkanol, 2-S-(tetrahydropyranyl)thioalkyl carboxylate, and their furanyl homologs, i.e., 5-S-(tetrahydrofuranyl)-thioalkanol and 5-S-(tetrahydrofuranyl)thioalkyl carboxylate.

[0002] This invention also relates to articles of manufacture such as rigid pipe and window profile, flexible film, and semi-rigid tubing that are prepared from such heat-stabilized vinyl chloride polymer compositions.

BACKGROUND OF THE INVENTION

[0003] It is well known that the physical properties of various organic polymers deteriorate and color changes take place during processing of the polymer and during exposure of formed polymer products to certain environments. Halogen-containing polymers are normally susceptible to heat-induced deterioration through autoxidation. The prime examples of such polymers are the vinyl and vinylidene polymers in which the halogen is attached directly to carbon atoms. Poly(vinyl chloride), copolymers of vinyl chloride and vinyl acetate, and poly(vinylidene chloride), the principal resin in self-clinging transparent food wraps, are the most familiar polymers which require stabilization for their survival during fabrication into pipe, window casings, siding, bottles, wall covering, packaging film, and the like. When such polymers are processed at elevated temperatures, undesirable color changes often occur within the first 5 to 10 minutes as well as during later stages of the processing. Haziness, which sometimes accompanies the color changes, is particularly undesirable where clear products are needed. The addition of heat stabilizers to such polymers has been absolutely essential to the wide-spread utility of the polymers. From a great deal of work in the development of more and more effective heat stabilizers there has emerged two principal classes: organotin compounds and mixed metal combinations. Organotin-based heat stabilizers are the most efficient and widely used stabilizers for rigid PVC. Synergistic combinations of alkyltin mercaptides and free mercaptans are particularly efficient heat stabilizers for rigid PVC during extrusion. They have not been entirely satisfactory, however, because of several failings on the part of the mercaptan synergist and are not used in flexible PVC. Many mercaptans give off an offensive odor even at room temperature and the odor grows worse at PVC processing temperatures. The oxidative stability of the mercaptans is very often very poor. Oxidation of the free mercaptans diminishes the synergism. A combination having an enhanced synergism would be welcomed especially by the flexible PVC industry. Also, because of the end-use of articles made from some polymers, many polymeric compositions require the presence of both biocides and heat stabilizers but the use of the organotin mercaptide/mercaptan combination in such a composition is often frustrated by the tendency of the free mercaptan to deactivate a biocide such as the much used OBPA (10, 10'-oxybisphenoxarsine).

[0004] Zinc salts in general have long been believed to be less satisfactory as heat stabilizers for halogen-containing polymers than the organotin-based stabilizers and, indeed, have lent their name to the catastrophic degradation known as zinc burn. In U.S. Patent No. 3,660,331, Ludwig teaches the stabilization of vinyl halide resins by certain thioethers and thioesters of tetrahydropyran. Better heat stabilizer compositions are still needed, however. The thioether/low level metallic stabilizer combinations of this invention satisfy that need.

SUMMARY OF THE INVENTION

[0005] It has now been found that the activity of the 2-S-(tetrahydropyranyl)thioalkanol, the carboxylates thereof, and their furanyl homologs as heat stabilizers in halogen-containing polymer compositions is unexpectedly higher than that predicted on the basis of sulfur content when used in conjunction with very low levels of a metal-based stabilizer or a Lewis acid. Zinc salts are particularly valuable as synergists of latent mercaptans in their function as heat stabilizers for halogen-containing polymers. Zinc chloride, a Lewis acid, is of particular interest as such a synergist.

[0006] It is an object of this invention, therefore, to provide a heat stabilizer composition having the synergy of a mercaptan plus improved oxidative stability.

[0007] It is another object of this invention to provide a halogen-containing polymer composition stabilized against

heat by 2-S-(tetrahydropyranyl)thioalkanols, carboxylates thereof, and their furanyl homologs in combination with a synergistic amount of a metal-based stabilizer or a Lewis acid.

[0008] It is another object of this invention to provide a PVC composition and article stabilized against heat by 2-S-(tetrahydropyranyl) thioalkanols, carboxylates thereof, and their furanyl homologs in combination with a synergistic amount of a metal-based stabilizer or a Lewis acid.

[0009] It is a related object of this invention to stabilize rigid, semi-rigid, and flexible PVC resin compositions with a heat stabilizer composition of this invention.

[0010] It is another object of this invention to provide a latent mercaptan-containing heat stabilizer composition which is substantially free from the offensive odor typically associated with mercaptans.

[0011] It is still another object of this invention to provide a flexible PVC composition and article stabilized against heat by a 2-S-(tetrahydropyranyl)thioalkyl carboxylate, its furanyl homolog, or a mixture thereof, in combination with a synergistic amount of a zinc salt.

[0012] These and other objects of the invention which will become apparent from the following description are achieved by adding a 2-S-(tetrahydropyranyl)thioalkanol, a carboxylate thereof, a furanyl homolog of either or both, or a mixture of two or more of said alkanols and esters, and a synergistic amount of a metal-based heat stabilizer or Lewis acid or a mixture of said metal-based heat stabilizer and Lewis acid to a halogen-containing polymer composition and processing the composition at an elevated temperature at which the latent mercaptan degrades to liberate a free mercaptan. The terms "latent mercaptan" and "blocked mercaptan" are used interchangeably herein.

[0013] Other products of the degradation of the blocked mercaptan are believed to include carbocations of the blocking moiety which are stabilized by a molecular structure in which the electron deficiency is shared by several groups. Resonance stabilization and neighboring group stabilization are two of the possible mechanisms by which the carbocations may be stabilized. The carbocations act as intermediates in the formation of stable compounds early in the hot processing of halogen-containing polymers. Although such mechanisms and the resultant carbocations are believed to be an impetus for the liberation of the active free mercaptan, this invention is in no way limited by the foregoing attempt to explain the working of the invention. Those skilled in the art will see the resonance stabilization and neighboring group stabilization that are possible in the following structures of the blocked mercaptan; other mechanisms may be at work in other blocked mercaptans represented by these structures that also liberate an active free mercaptan upon thermal and/or chemical degradation during processing of polymeric compositions containing such blocked mercaptans. For the purposes of this invention, the terms "blocked mercaptan" and "latent mercaptan" are used interchangeably to mean a thioether which degrades during processing of the composition at an elevated temperature to liberate a free mercaptan.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The term halogen-containing organic polymers as used herein means halogen-containing polymers or resins in which the halogen is attached directly to the carbon atoms. The halogen-containing polymers which can be stabilized according to this invention include chlorinated polyethylene having 14 to 75%, e.g. 27%, chlorine by weight, chlorinated natural and synthetic rubber, rubber hydrochloride, chlorinated polystyrene, chlorinated polyvinyl chloride, polyvinyl bromide, polyvinyl fluoride, and vinyl chloride polymers. The vinyl chloride polymers are made from monomers consisting of vinyl chloride alone or a mixture of monomers comprising, preferably, at least about 70% by weight of vinyl chloride, based on the total monomer weight. Examples of the copolymers include those made from vinyl chloride and from about 1 to about 30% of a copolymerizable ethylenically unsaturated material such as vinyl acetate, vinyl butyrate, vinyl benzoate, vinylidene chloride, diethyl fumarate, diethyl maleate, other alkyl fumarates and maleates, vinyl propionate, methyl acrylate, 2-ethylhexyl acrylate, butyl acrylate and other alkyl acrylates, methyl methacrylate, ethyl methacrylate, butyl methacrylate and other alkyl methacrylates, methyl alpha-chloroacrylate, styrene, trichloroethylene, vinyl ketones such as vinyl methyl ketone and vinyl phenyl ketone, 1-fluoro-2-chloroethylene, acrylonitrile, chloroacrylonitrile, allylidene diacetate, chloroallylidene diacetate, and vinyl ethers such as vinyl ethyl ether, vinyl chloroethyl ether, vinyl phenyl ether, and the vinyl ether prepared by the reaction of one mole of acrolein with one mole of ethylene glycol divinyl ether. Typical copolymers include vinyl chloride-vinyl acetate (96:4 sold commercially as VYNW), vinyl chloride-vinyl acetate (87:13), vinyl chloride-vinyl acetate-maleic anhydride (86:13:1), vinyl chloride-vinylidene chloride (95:5); vinyl chloride-diethyl fumarate (95:5), and vinyl chloride 2-ethylhexyl acrylate (80:20).

[0015] As used herein, the term PVC composition means a composition comprising a halogen-containing vinyl polymer in which the halogen is attached directly to a carbon atom. A rigid PVC composition is one which does not contain a plasticizer. A semi-rigid PVC composition is one which contains from 1 to about 25 parts of a plasticizer per 100 parts by weight of the halogen-containing vinyl polymer. A flexible PVC composition contains from about 25 to about 100 parts per 100 parts by weight of the halogen-containing vinyl polymer. Alkyl esters of carboxylic acids in which there are from 1 to 3 alkyl groups having from 8 to 12 carbon atoms are representative of the plasticizers. The alkyl group may be n-octyl, 2-ethylhexyl, nonyl, decyl, or dodecyl. Suitable esters include phthalates, trimellitates, benzoates,

adipates, glutarates, and sebacates. The plasticizer may also be a pentaerythritol or such an ester thereof. A polymeric plasticizer is also suitable.

[0016] As used herein, a hydrocarbyl radical contains from 1 to 20 carbon atoms and may be an alkyl, cycloalkyl, aryl, arylene, alkaryl, aralkyl, or an aralkenyl or alkenyl radical having up to 3 ethylene double bonds; likewise, said radicals constitute the hydrocarbyl portion of a hydroxyhydrocarbyl radical. As used herein: a mono-valent radical has but one valence available for combining with another radical whereas a di-valent radical may combine with two other radicals; the term alkyl represents monovalent straight or branched chain hydrocarbon radicals ; the term alkylenyl represents divalent, trivalent, and tetravalent straight or branched chain hydrocarbon radicals; the term oxyalkylenyl represents a divalent radical of a polyalkylene ether molecule having a polyalkoxy chain of from 2 to 4 of such radicals, wherein the alkylene moiety has 2 or 3 carbon atoms.

[0017] Also, as used herein: an acyloxyalkyl radical originates from a carboxylic acid ester of an alkyl alcohol; the R^1 radical in Formula 1 below, therefore, in the stearic acid ester of mercaptopropanol is the stearoyloxypropyl radical; likewise, the R^1 radical of the oleic acid ester of mercaptopropanol, which is one of the tallate esters of that alcohol, is the oleoyloxypropyl radical. The R^1 radical of lauryl-3-mercaptopropionate, on the other hand, is dodecyloxycarbonylpropyl.

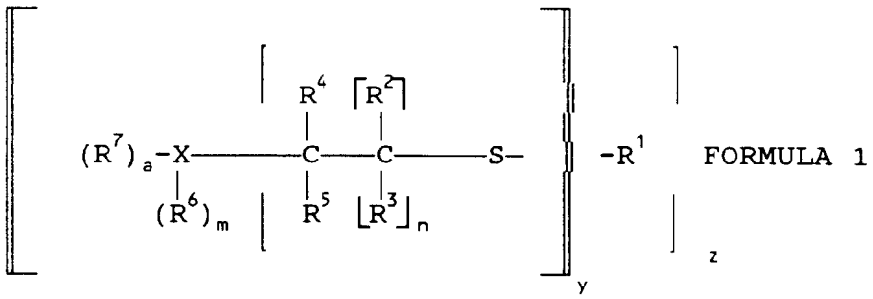
[0018] Substantially means largely if not wholly that which is specified but so close that the difference is insignificant.

[0019] The stabilizer compositions of this invention consist essentially of from about 87.5 % to about 98.5%, preferably from about 93.5 % to about 97.5 %, by weight of a 2-S-(tetrahydropyranyl)thioalkanol, a 2-S-(tetrahydrofuranyl) thioalkanol, a carboxylate of either or both, or a mixture of two or more of said alkanols and esters, based on the total weight of the stabilizer composition, the balance comprising the metal-based stabilizer or Lewis acid. They are particularly suited to impart superior stabilization against the deteriorative effects of heat and ultra-violet light on both rigid and flexible PVC resins in comparison with stabilizer compositions previously known in the art. They may be prepared by blending the components thereof in any convenient manner which produces a homogeneous mixture, such as by shaking or stirring in a container. Likewise, the stabilizer compositions of this invention can be incorporated in a halogen-containing polymer by admixing the components of the stabilizer composition and of the polymer composition, such as, for example, in an appropriate mill or mixer or by any other of the well-known methods which provide uniform distribution of the stabilizer throughout the polymer composition.

[0020] One of the advantages of this invention is that the offensive odor of mercaptans is masked by a blocking group so that the latent mercaptan thus created may be put into a PVC composition or the like with little or no offense to the operator with the knowledge that the free mercaptan will be released as a degradation product when the treated composition is heated during the usual processing, e.g. extrusion.

[0021] The blocking compounds are preferably those which are capable of furnishing a stabilized carbocation having a molecular structure in which the electron deficiency is shared by several groups. Resonance stabilization and neighboring group stabilization are two of the possible mechanisms by which the carbocations may be stabilized.

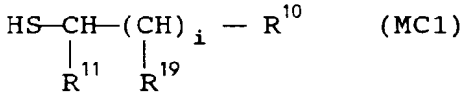
[0022] The blocked mercaptans suitable for the purposes of this invention are represented by FORMULA 1:



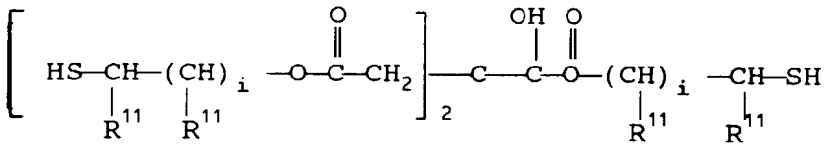
FORMULA 1

wherein a is 1, m is 0, n is 0 or 1; y is 1 or 2, and z is 1; R^1 is a hydroxyalkyl group, a hydroxy(polyalkoxy)alkyl group, an acyloxyalkyl group, an acyloxy(hydroxyalkyl) group, acyloxy(alkoxyalkyl) group, an alkylene bis-(acyloxyalkyl) group, a hydroxy(polyalkoxy) acylalkyl group, an acyloxy(polyalkoxy)alkyl group, an oxy[bis(alkoxyacylalkyl)] group, an oxy[bis(polyalkoxyacylalkyl] group, a benzoyloxy(polyalkoxy)alkyl group, or a benzoyloxy(polyalkoxy)acylalkyl group, in which the alkyl moieties have from 2 to 20 carbon atoms, and the acyloxy moiety has from 2 to 22 carbon atoms; R^2, R^3, R^4, and R^5 are hydrogen; and either R^3 or R^5 is joined with R^7 and O to form a heterocyclic moiety having 4 or 5 ring carbons with or without an alkoxy (C_1-C_4), aryloxy (C_6-C_{10}), alkaryloxy (C_7-C_{14}) or formyl substituent.

[0023] The mercaptans useful in this invention are the well-known mercaptoalkanols and mercaptocarboxylic acids and the esters of each. They include, but are not limited to, the following compounds:



(MC1)



(MC3)

wherein R^{10} and R^{19} are independently OH, -O(C=O)R^{17}
-(C=O)OR^{17}, -SH, aryl, C_1 to C_{18} alkyl, and -H;

R^{11} is -H, aryl, or C_1 to C_{18} alkyl;
R^{17} is -H, alkyl, alkenyl, aryl, aralkyl, alkaryl, cycloalkyl, or cycloalkylenyl;

wherein i=0 or an integer from 1 to 6 inclusive.

[0024] Mercaptan-containing organic compounds preferred as intermediates in the preparation of the latent mercaptans of this invention are those compounds according to formula (MC1) where R^{11} is -H, R^{19} is -H, R^{10} is -O(C=O) R^{17} or -(C=O)OR^{17}, and i=1; and those compounds according to formula (MC3) where R^{11} is -H and i=1.

[0025] Examples of mercaptan-containing compounds described by the above formulas include, but are not limited to, the following compounds:

$HSCH_2CH_2OH$

$HSCH_2CH2CH_2OH$

$HSCH_2COOH$

$HSCH_2COOC_8H_{17}$

$HSCH_2CH_2CH_2CH(OH)\ CH_2CH(OH)$

$HSCH_2CH_2OC(=O)\ C_{17}H_{33}$

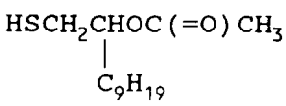
$HSCH_2CH_2CH_2OC(=O)\ C_8H_{17}$

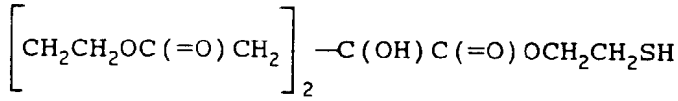
$HSCH_2CH_2OC(=O)\ CH{=}CHC(O=)\ OCH_2CH_2SH$

$HSCH_2CH_2OC(=O)\ C_{11}H_{23}$

$HSCH_2CH_2OC(=O)\ CH_2CH_2C(=O)\ OCH_2CH_2SH$

$HSCH_2CH_2OC(=O)(CH_2)_4C(=O)OCH_2CH_2SH$





[0026] In general, the procedure for making the latent mercaptans which are useful in this invention comprises adding the mercapto group of the free mercaptan across the double bonds of polarized, unsaturated compounds is as follows:

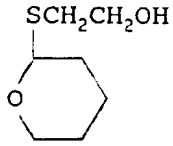
[0027] To a stirred mixture, under nitrogen atmosphere, of the mercaptan, acid catalyst, and optionally, a small percentage of antioxidant to inhibit radical reactions, is added dropwise to the polarized, unsaturated compound, either neat or in solution, while maintaining the temperature between 10°-70° C. The mixture or solution is then heated for between 1 and 6 hours at 35°-70° C and conversion to product is monitored by gas chromatography and iodine titration for SH. The acid catalyst is removed by an alkaline wash and the resulting product is dried with magnesium sulfate and filtered. The solvent, if required, is removed under reduced pressure at <50° C to yield the latent mercaptan. A solid phase catalyst may be used and then filtered out of the reaction mixture and regenerated for use in a subsequent synthesis, In this way, a wash step is eliminated.

[0028] The polarized, unsaturated compounds are exemplified by 3,4-dihydropyran; 3,4-dihydro-2-methoxy-2H-pyran; 3,4-dihydro-2-ethoxy-2H-pyran; 3,4-dihydro-2-phenoxy-2H-pyran; 3,4-dihydro-2-formyl-2H-pyran; and 2,3-dihydrofuran. The 3,4-dihydro-2-formyl-2H-pyran is made by the Diels-Alder dimerization of acrolein at high temperatures and pressures. The 3,4-dihydro-2-alkoxy-2H-pyrans and 3,4-dihydro-2-phenoxy-2H-pyran are made by the reaction of the corresponding vinyl ether with acrolein in the presence of a catalytic amount of a zinc salt, e.g., zinc chloride. A variety of 3,4-dihydro-2H-pyrans having a substituent in the 2-position can be made by similar reactions. The products formed by the reaction of 1 and 2 moles of acrolein with the divinyl ether of an alkylene- or polyalkylene glycol are blocking agents, also. The latent mercaptans made from the di-(3,4-dihydropyranyl) ethers also have the potential of being chelating agents in the polymer compositions of this invention. In the case of the reaction of one mole of acrolein per mole of a divinyl ether, the vinyl ether group of the resulting monomer permits the product to be incorporated into a vinyl chloride copolymer followed by the addition of a mercaptan across the double bond of the pyran ring to yield a latent mercaptan that is an integral stabilizer for the polymer. The reaction of one mole of acrolein with one mole of the divinyl ether also allows for the formation of a monomeric latent mercaptan of the mercaptan/tetrahydropyran adduct type in which the vinyl ether group of the resulting monomer permits the product to be copolymerized with one or more of a wide variety of ethylenically unsaturated compounds to form polymeric latent mercaptans. The product from the reaction of acrolein with chloroethyl vinyl ether provides a substituted 3,4-dihydropyran that can be further derivatized. The addition of a mercaptan across the double bond of the pyran ring can be done in the presence of the zinc salt catalyst to yield a stabilizer composition of this invention.

[0029] When 2-S-tetrahydopyranylthioethanol is prepared from 3,4-dihydropyran by said procedure, by-products having the following formulas (as each relates to FORMULA 1) are also obtained:

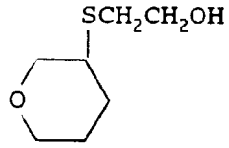
FORMULA

2.



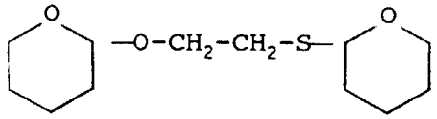
a = 1, m = 0, n = 0, y = 1, z = 1; X is oxygen, R^5 and R^7 join to form $-CH_2-CH_2-CH_2-CH_2-$; R^4 is hydrogen, and R^1 is hydroxyethyl.

3.



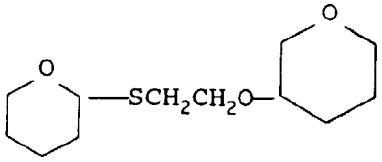
a = 1, m = 0, n = 1, y = 1, z = 1; X is oxygen, R^3 and R^7 join to form $-CH_2-CH_2-CH_2-$; R^2, R^4 and R^5 are hydrogen, and R^1 is hydroxyethyl.

4.



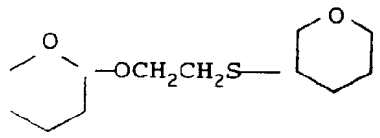
a = 1, m = 0, n = 0, y = 1, z = 1; X is oxygen, R^5 and R^7 join to form $-CH_2-CH_2-CH_2-CH_2-$; R^4 is hydrogen, and R^1 is 2-ethoxytetrahydropyranyl.

5.



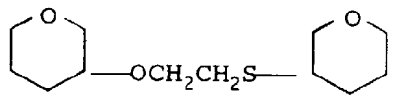
a = 1, m = 0, n = 0, y = 1, z = 1; X is oxygen, R^5 and R^7 join to form $-CH_2-CH_2-CH_2-CH_2-$; R^4 is hydrogen, and R^1 is 3-ethoxytetrahydropyranyl.

6.



a = 1, m = 0, n = 1, y = 1, z = 1; X is oxygen, R^3 and R^7 join to form $-CH_2-CH_2-CH_2-$; R^2, R^4 and R^5 are hydrogen, and R^1 is 2-ethoxytetrahydropyranyl.

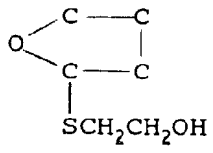
7.



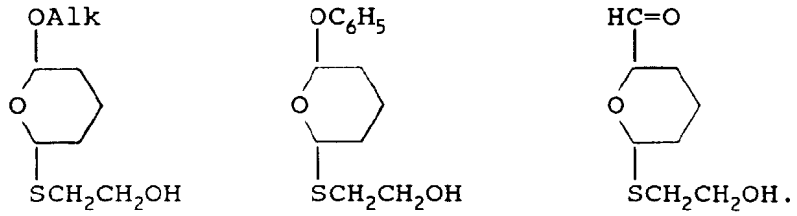
a = 1, m = 0, n = 1, y = 1, z = 1; X is oxygen, R^3 and R^7 join to form $-CH_2-CH_2-CH_2-$; R^2, R^4 and R^5 are hydrogen, and R^1 is 3-ethoxytetrahydropyranyl.

[0030] The homologous by-products are expected when 2,3-dihydrofuran is reacted with mercaptoethanol but the principal product is the 5-S-tetrahydrofuranylthioethanol shown by the following structure:

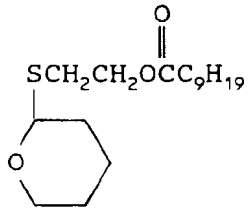
8.



[0031] When the 3,4-dihydropyran is replaced by a 3,4-dihydro-2-alkoxy-pyran; a 3,4-dihydro-2-phenoxy-pyran; or a 3,4-dihydro-2-formyl-pyran in the above procedure, the following products are formed:



[0032] Examples of 2-S-(tetrahydropyranyl)thioalkanols that are suitable as latent mercaptans for this invention include, without limitation, 2-S-(tetrahydropyranyl)thioethanol, 2-S-(tetrahydropyranyl)thiopropanol, and 2-S-(tetrahydropyranyl)-thiobutanol. The carboxylates suitable for the purposes of this invention are exemplified by 2-S-(tetrahydropyranyl)thioethyl caprate, which also may be named 2-S-(2-decanoyloxyethylthio) tetrahydropyran, made by the reaction between mercaptoethyl caprate and 3,4-dihydropyran according to the foregoing procedure and has the following formula in relation to FORMULA 1:



wherein a = 1, m = 0, n = 0; y = 1, z is 1; X is oxygen, R^5 and R^7 are joined to form $-CH_2-CH_2-CH_2-CH_2-$; R^4 is hydrogen, and R^1 is decanoyloxyethyl.

[0033] Homologs of the thus described compounds which are particularly useful in the stabilization of flexible PVC compositions include the 2-S-(tetrahydropyranyl)thioalkyl carboxylates and their furanyl homologs wherein the ethyl moiety is replaced by propyl, butyl, hexyl, and others in the series up to and including dodecyl and the capric acid radical of said compound is replaced by other fatty acid radicals (saturated and unsaturated) or resin acid radicals having up to and including 22 carbon atoms. The acids are exemplified by caproic, caprylic, lauric, myristic, palmitic, stearic, arachidic, behenic, and the oleic and linoleic acids, as such, or as found in tall oil acids along with abietic and pimaric acids. The mercaptoalkyl carboxylate moiety is thus exemplified by mercaptoethyl laurate, mercaptoethyl oleate, mercaptoethyl hexanoate, mercaptoethyl octanoate, mercaptoethyl myristate, mercaptoethyl palmitate, mercaptoethyl stearate, and the mercaptopropyl, mercaptobutyl, and mercaptooctyl homologs of each of the above. The esters are made by the conventional method of reacting the hydroxyl group of a mercaptoalkanol with the desired carboxylic acid in the presence of an acidic catalyst and removing water as it forms.

[0034] The 2-S-(tetrahydropyranyl)thioalkanols, the carboxylates thereof, and their furanyl homolgs are employed in this invention in an amount sufficient to impart the desired resistance to heat deterioration to halogen-containing organic polymers. It will be readily apparent to one of ordinary skill in the art, that the precise amount of stabilizer composition used will depend upon several factors, including, but not limited to, the particular halogen-containing organic polymer employed, the temperature to which the polymer will be subjected, and the possible presence of other stabilizing compounds. In general, the more severe the conditions to which the halogen-containing organic polymer is subjected, and the longer the term required for resisting degradation, the greater will be the amount of stabilizer composition required. Generally, as little as about 0.20 part by weight of the latent mercaptan per hundred parts by weight of the PVC resin will be effective. While there is no critical upper limit to the amount of latent mercaptan which can be employed, amounts of about 3.0 parts or less by weight per hundred parts of the PVC resin are preferred.

[0035] A 2-S-(tetrahydropyranyl)mercaptoalkyl carboxylate is more active as a heat stabilizer in flexible PVC compositions than the tetrahydropyranyl-blocked mercaptans derived from alkylmercaptans such as dodecanethiol when activated according to this invention as manifest in the improved color hold properties and dynamic thermal stability of such stabilized PVC compositions. The higher activity may be the result of the better compatibility of the ester-containing latent mercaptans with a plasticized PVC. The compatibility of the corresponding homologous furan-based latent mercaptans is similar.

[0036] Metallic-based stabilizers are defined for the purposes of this invention as metal salt stabilizers, organometallic stabilizers. For the purposes of this invention, metal salts are defined to include oxides, hydroxides, sulfides, sulfates,

chlorides, bromides, fluorides, iodides, phosphates, phenates, perchlorates, carboxylates, and carbonates. The metal salt stabilizers are exemplified by zinc, barium, strontium, calcium, tin, magnesium, cobalt, nickel, titanium, antimony, and aluminum salts of hydrochloric acid, sulfuric acid, phenols, aromatic carboxylic acids, fatty acids, epoxidized fatty acids, oxalic acid, acetic acid, and carbonic acid. Calcium stearate, calcium 2-ethylhexanoate, calcium octoate, calcium oleate, calcium ricinoleate, calcium myristate, calcium palmitate, calcium laurate, barium laurate, barium stearate, barium di(nonylphenolate), magnesium stearate, zinc octoate (or caprylate), zinc 2-ethylhexanoate, zinc stearate, zinc laurate, zinc oxide, zinc chloride, zinc hydroxide, zinc sulfide, zinc sulfate, zinc bromide, and Group I and II metal soaps in general are examples of suitable salts along with tin stearate, aluminum stearate, and hydrotalcite. The synergistic amount of the metallic-based stabilizer is from about 0.01 to less than 0.5%, preferably 0.02-0.4%, and more preferably 0.03-0.1% by weight of the halogen containing resin. The zinc salts are much preferred because they provide not only dynamic stability to the heat processed resin but also superior color hold properties in comparison with the other metal salts, especially at very low concentrations such as from 0.03 to 0.1 %.

[0037] The Lewis acids are exemplified by boron trifluoride, aluminum chloride, zinc chloride and methyltin trichloride. Thus, there is some overlap between the metal salts and Lewis acids that are useful in this invention. The synergistic amounts of the Lewis acids for the purposes of this invention are from about 0.005 to less than 0.5%, preferably from about 0.01, more preferably from about 0.03, to about 0.1 % by weight of the halogen-containing resin. The Lewis acids and the metallic-based stabilizers may be used in combination.

[0038] Conventional organometallic stabilizers include the organotin carboxylates and mercaptides. Such materials include butyltin tris dodecyl mercaptide, dibutyltin dilaurate, dibutyltin didodecyl mercaptide, dianhydride tris dibutylstannane diol, dihydrocarbontin salts of carboxy mercaptals such as those set forth in Hechenbleikner et al.(U.S. Pat. No. 3,078,290). There can be included any of the vinyl chloride resin stabilizers set forth in Salyer (U.S. Pat. No. 2,985,617).

[0039] Monosulfides and/or polysulfides of the organotin mercaptides of carboxylates and/or mercaptoalkyl carboxylates and of alkyl thioglycolates are also suitable as metal based stabilizers in the compositions of this invention for improving the resistance of halogen-containing polymers to deterioration when heated to 350°F (177°C) during processing. The sulfides may be made by heating stoichiometric quantities of a mercaptoalkyl ester of a carboxylic acid or an alkyl mercaptocarboxylate and an organotin chloride having the formula:

$$R'_{(4-z)}SnHal_z \qquad II$$

wherein R' is an alkyl group having from 1 to 12 carbon atoms, Hal is a halogen having an atomic weight of from 35 to 127, preferably chlorine, and z is any number from 1 to 3; in water and ammonium hydroxide to about 30°C (86°F), slowly adding an alkali metal mono- or polysulfide, and heating the reaction mixture further to about 45°C before separating the product from said mixture.

[0040] Alternatively, the sulfide may be made by mixing a monoalkyl- or dialkyltin sulfide with an organotin mercaptide and by other procedures well known in the stabilizer art.

[0041] The sulfides of a mercaptoalkyl ester of a carboxylic acid are characterized by an equilibrium mixture of one or more alkyltin halides of Formula II, one or more mercaptides of Formula III and one or more alkyltin mono- or polysulfides or oligomers thereof, the alkyltin mono- and polysulfides having the formula IV.

$$R^{*}_{(4-n)}\text{-}Sn\text{-}[[S\text{-}Z\text{-}[OC(=O)R^{1*}]_m]]_n \qquad \text{Formula III}$$

wherein R^* is an alkyl radical having from 1 to 12 carbon atoms; R^{1*} is hydrogen, a hydrocarbyl radical, a hydroxyhydrocarbyl radical, or $R^{2*}C(=O)OR^{3*}$, wherein R^{2*} is alkylene, hydroxyalkylene, phenylene, or -CH=CH-, and R^{3*} is hydrogen, a hydrocarbyl radical, a hydroxyhydrocarbyl radical, or an alkylcarboxyalkylene radical; Z is an alkylene or hydroxyalkylene radical of at least 2 carbon atoms up to 20 carbon atoms; m is an integer from 1 to 3, n is from 2 to 3, and the valency of Z is m + 1.

[0042] Formula IV is representative of linear structures as well as of cyclic trimers and adamantyl rings:

$$[R^{4*}_{(4-x)}SnS_{(p/2)}]_M - [R^{5*}_{(4-y)}SnS_{(q/2)}]_N \qquad \text{Formula IV}$$

wherein R^{4*} and R^{5*} are independently alkyl radicals having from 1 to 12 carbon atoms and are bonded to Sn; x is 2 or 3; y is 2 or 3; p and q are 2 to 20, preferably 2-4; and M and N are 0-10, preferably 0-4, but $M \neq N = 0$; with the proviso that when (4-x)=(4-y), p=q, and when (4-x)≠(4-y), p#q.

[0043] It should be understood that the structures of the sulfides produced by the processes mentioned above are very complex. The reactions are believed to produce an equilibrium mixture composed of several different but related products. As will be appreciated by those of ordinary skill in chemistry, equilibrium mixtures inherently include the starting materials as well as the products of any reaction between them. The chemical and patent literature contain numerous examples demonstrating that members of different classes of organotin compounds may react with one another under certain conditions to yield products containing one or more tin atoms wherein at least a portion of the tin atoms are bonded to different combinations of radicals than they were before being mixed together. Accordingly, the sulfides are believed to include bis[monoorganotin)-bis (thioalkyl carboxylate)] monosulfides and polysulfides, bis [(diorganotin)-mono(thioalkyl carboxylate)]monosulfides and polysulfides, and products which arise during equilibrium reactions among said mono- and polysulfides, including monoalkyltin tris(thioalkyl carboxylates), dialkyltin bis(thioalkyl carboxylates), mono- and di-organotin mono- and polysulfides, and oligomers thereof, as well as the starting materials themselves. The sulfide of an alkyl ester of a mercaptocarboxylic acid is likewise believed to include bis[monoorganotin)-bis(alkyl mercaptocarboxylate)] monosulfides and polysulfides, bis[(diorganotin)-mono(alkyl mercaptocarboxylate)]monosulfides and polysulfides, and products which arise during equilibrium reactions among said mono- and polysulfides, including monoalkyltin tris(alkyl mercaptocarboxylates), dialkyltin bis(alkyl mercaptocarboxylates), mono- and di-organotin mono- and polysulfides, and oligomers thereof.

[0044] The polysulfides include mixtures of compounds having from 2 to 10 sulfur atoms linked together. Mixtures of monosulfides and polysulfides having from 2 to 4 sulfur atoms are preferred.

[0045] Conventional non-metallic stabilizers and antioxidants can also be included in the PVC compositions of the present invention. Thus, there can be included 0.01-0.75 %, based on the weight of the resin, of sulfur containing compounds such as dilauryl-thiodipropionate, distearyl 3,3'-thiodipropionate, dicyclohexyl-3,3-thiodipropionate, dioleyl-3,3'-thiodipropionate, dibenzyl-3,3'-thiodipropionate, didecyl-3,3'-thiodipropionate, dibenzyl-3,3'-thiodipropionate, diethyl-3,3'-thiopropionate, lauryl ester of 3-methylmercaptopropionic acid, lauryl ester of 3-butylmercaptopropionic acid, lauryl ester of 3-lauryl mercaptopropionic acid, and phenyl ester of 3-octyl mercaptopropionic acid.

[0046] In addition to the stabilizer compositions of this invention, the PVC compositions of this invention may contain plasticizers, as mentioned above in regard to flexible PVC, and conventional additives such as pigments, fillers, blowing agents, dyes, ultraviolet light absorbing agents, antioxidants, densifying agents, biocides, and the like.

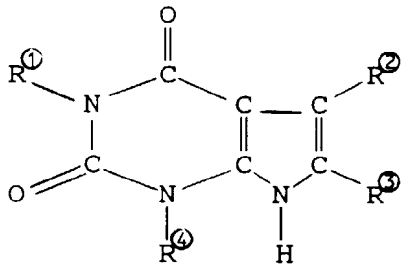
[0047] An antioxidant may be added in an amount of 0.01-10%, preferably 0.1-5% by weight of the PVC resin. Phenolic antioxidants are particularly suitable and are exemplified by 2,6-di-t-butyl-p-cresol, butylated hydroxyanisole, propyl gallate, 4,4'-thiobis(6-t-butyl-m-cresol), 4,4'-cyclohexylidene diphenol, 2,5-di-t-amyl hydroquinone, 4,4'-butylidene bis(6-t-butyl-m-cresol), hydroquinone monobenzyl ether, 2,2'-methylene-bis(4-methyl-6-t-butyl phenol), 2,6-butyl-4-decyloxy phenol, 2-t-butyl-4-dodecyloxy phenol, 2-t-butyl-4-dodecyloxy phenol, 2-t-butyl-4-octadecyloxy phenol, 4,4'-methylene-bis(2,6-di-t-butyl phenol), p-amino phenol, N-lauryloxy-p-amino phenol, 4,4'-thiobis(3-methyl-6-t-butyl phenol), bis [o-(1,1,3,3-tetramethyl butyl)phenol] sulfide, 4-acetyl-β-resorcylic acid, A-stage p-t-butylphenol-formaldehyde resin, 4-dodecyloxy-2-hydroxybenzophenone, 3-hydroxy-4-(phenylcarbonyl) phenyl palmitate, n-dodecyl ester of 3-hydroxy-4-(phenyl carbonyl) phenoxyacetic acid, and t-butyl phenol.

[0048] From 0.01-30% by weight of an epoxy compound, based on the weight of the vinyl chloride polymer in the PVC compositions of this invention may also be used. Examples of such epoxy compounds include epoxidized soya bean oil, epoxidized lard oil, epoxidized olive oil, epoxidized linseed oil, epoxidized castor oil, epoxidized peanut oil, epoxidized corn oil, epoxidized tung oil, epoxidized cottonseed oil, epichlorhydrin/bis-phenol A resins, phenoxy-propylene oxide, butoxypropylene oxide, epoxidized neopentylene oleate, glycidyl epoxystearate, epoxidized α-olefins, epoxidized glycidyl soyate, dicyclopentadiene dioxide, epoxidized butyl toluate, styrene oxide, dipentene dioxide, glycidol, vinyl cyclo-hexene dioxide, glycidyl ether of resorcinol, glycidol ether of hydroquinone, glycidyl ether of 1,5-dihyroxynaphthalene, epoxidized linseed oil fatty acids, allyl glycidyl ether, butyl glycidyl ether, cyclohexane oxide, 4-(2,3-epoxypropoxy) aceto-phenone, mesityl oxide epoxide, 2-ethyl-3-propyl glycidamide, glycidyl ethers of glycerine, pentaerythritol and sorbitol, and 3,4-epoxycyclohexane-1,1-dimethanol bis-9,10-epoxystearate. Likewise there can be used organic phosphites in an amount of 0.01 to 10%, preferably 0.1-5% by weight of the vinyl chloride polymer. The organic phosphites contain one or more, up to a total of three, aryl, alkyl, aralkyl and alkaryl groups, in any combination. The term "trialkylaryl" is inclusive of alkyl, aryl, alkaryl and aralkyl phosphites containing any assortment of alkyl, aryl, alkaryl and aralkyl groups. Exemplary are triphenyl phosphite, tricresyl phosphite, tri(dimethylphenyl) phosphite, tributyl phosphite, trioctyl phosphite, tridodecyl phosphite, octyl diphenyl phosphite, dioctyl phenyl phosphite, tri(octyl-phenyl) phosphite, tri(nonylphenyl) phosphite, tribenzyl phosphite, butyl dicresyl phosphite, octyl di(octyl-phenyl) phosphite, tri (2-ethyl-hexyl) phosphite, tritolyl phosphite, tri(2-cyclohexylphenyl) phosphite, tri-alpha-naphthyl phosphite, tri(phenyl-phenyl) phosphite, and tri(2-phenylethyl) phosphite.

[0049] Likewise there can be included from 0.01-10% by weight of the vinyl chloride polymer of a polyol stabilizer for vinyl chloride resins. Thus there can be included glycerol, sorbitol, pentaerythritol, mannitol and polyethers such as diethylene glycol, triethylene glycol, tetraethylene glycol, tripropylene glycol, and the like.

[0050] Nitrogen containing stabilizers such as dicyandiamide, melamine, urea, formoguanamine, dimethyl hydantoin,

guanidine, thiourea, 2-phenylindoles, aminocrotonates, N-substituted maleimides, uracil, the 1,3-dialkyl-6-amino-uracil derivatives described in German Offenlegungsschrift 19,741,778 by Ciba Specialty Chemicals Holding Inc., and the pyrrolodiazine diones described in published Australian Patent Application No. AU-A-48232/96 by Ciba-Geigy, and the like also can be included in amounts of 0.1-10% by weight. Of particular interest are the pyrrolodiazine diones described by the formula:



wherein , $R^{①}$, $R^{②}$, $R^{③}$, and $R^{④}$ are independently hydrogen or C_1-C_4 alkyl. Examples of compounds contemplated for use in this invention include the lH-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-diones exemplified by Compound Nos. 103, 111, 123, 129, and 131 of said Australian Patent Application, which have the following substituents:

No. 103	1,3,6-trimethyl;
No. 111	1,3,6,7-tetramethyl;
No. 123	none;
No. 129	1,3-diethyl,6-methyl;
No. 131	1,3-di-n-butyl,6-methyl;

[0051] Said compounds may be prepared by the method described by S. Senda and K. Hirota, Chem. Pharm. Bull., 22(7), 1459-1467(1974) or by the reaction of the corresponding aminouracil with molar excesses of chloroacetaldehyde and ammonium acetate in water at about 65°C until a precipitate forms or with molar excesses of acetoxyacetone and ammonium acetate in water at reflux for 12 hours. The German Offenlegungsschrift 19,741,778 and the Australian Patent Application No. AU-A-48232/96 are each incorporated herein by reference.

[0052] Conventional lubricants for vinyl chloride resins such as low molecular weight polyethylene, i.e. polyethylene wax, fatty acid amides, e.g. lauramide and stearamide, bisamides, e.g. decamethylene, bis amide, and fatty acid esters, e.g. butyl stearate, glyceryl stearate, linseed oil, palm oil, decyloleate, corn oil, cottonseed oil, hydrogenated cottonseed oil, stearic acid, calcium stearate, mineral oil, montan wax, oxidized polyethylene and the like can also be included.

[0053] The following examples further illustrate the preparation of blocked mercaptans of this invention, the preparation of stabilizer compositions of this invention, and the advantages of said blocked mercaptans and stabilizer compositions.

EXAMPLE 1 Y

[0054] ^{1}H-NMR spectroscopy was used to determine the molecular structure of 2-S-(decanoyloxyethylthio)tetrahydropyran or 2-S-(tetrahydropyranyl)thioethylcaprate which was prepared by adding 42.0 grams (0.50 mole) of 3,4-dihydropyran to 112.2 grams (0.50 equivalent) of mercaptoethylcaprate (14.7 % SH) in the presence of an acid catalyst over a period of 45 minutes while maintaining a nitrogen atmosphere and a temperature below 35 °C and then heating it to 50°C and holding that temperature for 1.5 hours. After cooling the solution, it was washed with two 200 ml portions of a 10 % sodium bicarbonate solution in water, followed by a 200 ml wash with water. The organic layer was dried with $MgSO_4$ to yield a light yellow liquid having an SH content of less than 0.5 percent as determined by titration with a 0.100 N iodine solution in isopropanol. The ^{1}H-NMR ($CDCl_3$, δ) spectrum was: 2.3 (2H, t, -C(=O)-C<u>H</u>$_2$-CH$_2$), 2.8 (2H, m, -S-C<u>H</u>$_2$-CH$_2$-), 4.2 (2H, m, -S-CH$_2$C<u>H</u>$_2$-O-), 4.9 (1H, m, -O-C<u>H</u>(-S-CH$_2$-)-CH$_2$-CH$_2$-). The total color change (dE) of a PVC composition containing 0.13 phr of the latent mercaptan of this example was measured versus a white tile standard using a Hunter colorimeter at one minute intervals. At one minute, it was 4.2; at five minutes, it was 8.4.

Example 2

[0055] 2-S-tetrahydropyranyl) thioethyltallate was prepared by adding 172.45 grams (2.05 equiv.) of 3,4-dihydro(2H)

pyran dropwise to 760.00 grams (2.00 equiv.) of 2-mercaptoethyltallate (8.70% SH by iodometric titration) containing 0.93 gram of methanesulfonic acid (70% active) over a period of 45 minutes under a nitrogen blanket and a temperature between 25-35°C and heating to 35-40°C for 2 hours. After cooling the solution, 3 grams of Norite carbon black was charged and the product was vacuum filtered to yield 932 grams of yellow liquid having a SH content of less than 0.4% as determined by titration with 0.100 N iodine solution in isopropanol. The ^{1}H-NMR(CDC13,δ) spectrum was: 2.3 (2H, t, -C(=O)-C$\underline{H}_2$-CH$_2$-), 2.8 (2H, m, -S-C$\underline{H}_2$-CH$_2$-), 4.3 (2H, m,(-CC(=O)-O-C$\underline{H}_2$), 4.9 (1H, m, -O-C$\underline{H}$(-S-CH$_2$)-CH$_2$-CH$_2$-). GC of the product (1% in ether) indicated one primary product peak at 26.3 minutes retention time (50-300°C; 10°C/min.; split flow injector/FID).

Examples 3-11

[0056] A general flexible PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=70)	100.0 parts
Dioctyl phthalate	40.0 phr
Epoxidized soybean oil	5.0 phr
Stearic acid 2-S-(tetrahydropyranyl thioethyl tallate)	0.2 phr
Metal carboxylate at equal levels of metal	See Table I

was processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 350°F with chips taken at five minute intervals to a maximum of 60 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table II. The dynamic thermal stability (DTS) of the compositions was measured on a Brabender Plasti-Corder PL-2000 at 200°C/80rpm with No.6 roller blades and an electric head. The DTS, shown in Table III was recorded as the time in minutes before a sharp upturn in the torque curve during processing was observed.

[0057] As the data in the tables shows, all of the compositions have good dynamic stability but those containing zinc carboxylates have both dynamic stability and excellent color hold.

TABLE I

Example	Metal Carboxylate	Amount (phr)
Control	None	---
3	Nickel stearate	0.10
4	Zinc stearate	0.09
5	Zinc Octoate	0.05
6	Tin (II) stearate	0.05
7	Barium stearate	0.05
8	Cadmium stearate	0.06
9	Lead (II)stearate	0.03
10	Aluminum stearate	0.30
11	Calcium stearate	0.14

TABLE II

PVC Color Hold (Yellowness Index)												
Minutes												
Time\ Ex.	5	10	15	20	25	30	35	40	45	50	55	60
Cntrl.	47.1	77.2	89.1	101.0	94.3	99.7	105.4	99.9	98.1	93.9	94.2	89.8

TABLE II (continued)

PVC Color Hold (Yellowness Index)												
Minutes												
Time\ Ex.	5	10	15	20	25	30	35	40	45	50	55	60
3	54.3	80.5	93.5	103	107.7	112.1	107.8	111.6	119.9	111.8	103.5	119.8
4	9.0	12.3	11.8	13.4	16.6	17.2	21.0	24.6	30.8	39.8	48.1	53.2
5	9.7	11.7	13.9	14.5	15.6	16.8	20.6	22.9	23.8	31.1	35.8	40.5
6	50.5	89.2	96.9	94.9	106.9	106.6	107.9	105.0	98.7	105.4	102.0	107.1
7	51.0	86.6	108.5	116.6	115.6	118.8	135.0	134.6	135.4	138.4	126.1	133.5
8	16.0	41.7	47.9	51.2	52.2	54.8	56.6	60.9	65.7	70.9	72.1	83.2
9	25.4	56.8	78.2	82.6	88.6	95.6	103.9	96.7	96.1	101.2	99.9	107.1
10	51.3	73.5	81.4	87.2	93.0	98.8	101.3	106.0	111.4	116.1	116.6	119.2
11	51.9	80.8	93.2	109.5	118.4	126.7	126.7	143.0	137.6	141.3	142.3	139.6

Table III

Dynamic Thermal Stability	
Example	Time/minutes
Control	43.9
3	43.8
4	40.4
5	45.0
6	51.4
7	53.5
8	48.2
9	50.5
10	45.9
11	61.6

Examples 12-15

[0058] In this example, the relationship between the compatibility of the mercaptoalkyl esters with the plasticized vinyl chloride resin and their stabilizing power is shown.

[0059] A general flexible PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=70)	100.0 parts
Dioctyl phthalate	40.0 phr
Epoxidized soybean oil	5.0 phr
Stearic acid	0.2 phr
Zinc octoate (18% Zn)	0.05 phr
2-S-(tetrahydropyranyl thioethylcarboxylate)	See Table IV

was processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 350°F with chips taken at five minute intervals to a maximum of 60 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table V.

TABLE IV

Example	Carboxylate	% sulfur	Amount (phr)
12	Hexanoate	12.4	1.6
13	Caprate	10.4	1.9
14	Tallate	7.6	2.6
15	Oleate	7.6	2.6
Control	None (alcohol)	19.8	1.0

Table V

PVC Color Hold (Yellowness Index)												
Minutes												
	5	10	15	20	25	30	35	40	45	50	55	60
12	10.5	11.1	11.8	13.5	14.7	20.5	25.5	31.0	38.1	49.8	60.5	69.5
13	10.5	11.0	10.9	13.4	14.1	16.4	20.6	24.0	30.7	32.1	44.8	57.1
14	11.2	12.4	14.1	14.9	16.5	17.9	19.0	21.8	23.9	24.5	29.5	32.1
15	10.0	11.6	12.7	13.3	14.7	14.9	16.2	19.1	22.5	25.6	33.6	40.7
Cntrl.	10.4	11.9	13.0	14.3	16.6	20.4	23.8	27.3	34.5	38.2	48.0	62.1

Examples 16-17 and Comparative Example 1

[0060] The general flexible PCV formulation of Examples 12-15, was modified as shown in Table VI, and the resulting compositions were processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 350°F with chips taken at five minute intervals to a maximum of 60 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table VII. They were also processed on a Brabender Plasti-Corder PL-2000 with electric mixing heads (roller type 6) at 200°C/80 rpm to measure their dynamic thermal stability (DTS). The DTS, shown in Table VIII, was recorded as the time in minutes before a sharp upturn in the torque curve during processing was observed.

Table VI

Stabilizer Systems Evaluated			
Reference phr	Stabilizer	ppm Metals	Use Level,
Control 1	2-S-(tetrahydropyranyl)thioethyltallate	none	2.05
Control 2	Zinc octoate (18% as zinc)	2,506	2.05
16	2-S-(tetrahydropyranyl)thioethyltallate Zinc octoate (18% as zinc)	--- 61	2.00 0.05 2.05
17	Mark 859 2-S-(tetrahydropyranyl)thioethyltallate	706 ----	1.00 1.05
Comp. Ex. 1	Mark 859	1,448	2.05

Table VII

PVC Color Hold (Yellowness Index) During Processing by Two-Roll Mill @ 350°F												
	Minutes											
	5	10	15	20	25	30	35	40	45	50	55	60
C1	42.0	68.8	88.9	93.7	99.0	95.1	99.0	91.3	96.8	96.9	101.4	104.4
C2	12.2	15.4	22.6	19.4	burn	---	---	---	---	---	---	---
16	10.5	11.4	12.0	12.8	14.7	16.4	17.5	19.3	21.1	22.2	27.8	34.3
17	11.3	13.5	15.8	18.3	20.1	20.2	20.9	22.1	20.5	19.4	22.1	28.8
CE	10.6	11.6	11.3	11.9	13.3	15.3	18.5	23.1	30.2	35.5	49.7	49.7
C1=Control 1; C2=Control 2; CE=Comparative Example 1												

Table VIII

PVC Dynamic Thermal Stability by Brabender @200°C	
Control 1	52.3 minutes
Control 2	3.7 minutes
16	38.5 minutes
17	52.3 minutes
Comparative Example 1	39.3 minutes

Example 18

[0061] This example demonstrates the use of a Lewis acid such as zinc chloride in synergy with latent mercaptans.

[0062] A general flexible PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=70)	100.0 parts
Dioctyl phthalate	40.0 phr
Epoxidized soybean oil	5.0 phr
Stearic acid	0.2 phr

was modified as shown in Table IX and the resulting compositions were processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 350°F with chips taken at five minute intervals to a maximum of 60 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table X.

Table IX

Stabilizer Systems Evaluated		
Reference	Stabilizer	Use Level, phr
Control 1	2-S-(tetrahydropyranyl)thioethyltallate	2.02
Control 2	Zinc chloride (anhydrous)	0.02
18	2-S-(tetrahydropyranyl)thioethyltallate Zinc chloride (anhydrous)	2.00 0.02

Table X

PVC Color Hold (Yellowness Index) During Processing by Two-Roll Mill @ 350°F												
min/ex	5	10	15	20	25	30	35	40	45	50	55	60
C1	48.5	90.6	106.8	115.9	121.2	132.2	127.3	122.6	113.9	110.5	98.8	84.2
C2	18.3	26.7	46.1	68.8	45.2	burn	---	---	---	---	---	---
18	14.9	16.1	18.1	19.8	20.8	22.4	23.6	26.5	26.0	26.3	28.2	28.9

Examples 19-20 and Comparative Example 2

[0063] Whereas the surprising effect of very low levels of metallic-based stabilizers on 2-S-(tetrahydropyranyl)thioalkyl carboxylates in flexible PVC compositions has been shown above, the role played by the better compatibility of a 2-S-(tetrahydropyranyl)thioalkanol in combination with such low levels of metallic-based stabilizers in a rigid PVC is shown in the following examples.

[0064] A conventional rigid PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=65)	100.0 parts
Calcium carbonate	5.00 phr
Titanium dioxide	1.0 phr
Calcium stearate	0.6 phr
Paraffin wax	1.2 phr
Oxidized polyethylene	0.15 phr

was modified as shown in Table XI and the resulting compositions were processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 390°F with chips taken at one minute intervals to a maximum of 12 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table XII. The DTS, measured as described above but at 190°C, is shown in Table XIII.

Table XI

Stabilizer Systems Evaluated		
Reference	Stabilizer	Use Level, phr
Comp. Ex. 2	ADVASTAB TM-694 stabilizer*	0.40
19	2-S-(tetrahydropyranyl)thioethanol** Zinc octoate (18% zinc)l	2.50 0.05
20	2-S-(tetrahydropyranyl)thioethyltallate Zinc octoate (18% zinc) Dibenzoylmethane	2.00 0.05 0.05

*ADVASTAB is a registered trademark of Morton International, Inc.

** includes minor amounts of compounds of Formulas 3-7.

Table XII

PVC Color Hold (Yellowness Index) During Processing by Two-Roll Mill @ 390°F												
min/ex	1	2	3	4	5	6	7	8	9	10	11	12
CE 2	3.0	3.9	4.5	5.1	5.8	7.2	9.3	11.5	14.2	16.8	18.6	21.5
19	4.8	7.4	7.9	7.6	7.3	7.7	7.8	9.8	12.8	16.5	20.5	24.4
20	4.3	5.9	9.0	11.9	14.0	15.9	17.1	17.4	16.4	18.3	21.9	26.3

Table XIII

PVC Dynamic Thermal Stability by Brabender @190°C	
	Minutes
Comparative Example 2	6.3
19	18.0
20	6.1

Examples 21-22 and Comparative Examples 3-4

[0065] The activating effect of a Lewis acid and of a metallic-based stabilizer on a latent mercaptan according to this invention, when used alone and in combination, is shown in this example.

[0066] A conventional rigid PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=65)	100.0 parts
Calcium carbonate	5.00 phr
Titanium dioxide	1.0 phr
Calcium stearate	0.6 phr
Paraffin wax	1.2 phr
Oxidized polyethylene	0.15 phr

was modified as shown in Table XIV and the resulting compositions were processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 390°F with chips taken at one minute intervals to a maximum of 11 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table XV.

Table XIV

Stabilizer Systems Evaluated		
Reference	Stabilizer	Use Level, phr
Comp. Ex. 3	ADVASTAB TM-599T*	0.25
Comp. Ex. 4	ADVASTAB TM-599T* Methyltin trichloride	0.235 0.015
21	2-S-(tetrahydropyranyl)thioethanol** ADVASTAB TM-599T* Methyltin trichloride	0.05 0.235 0.015
22	2-S-(tetrahydropyranyl)thioethanol ** ADVASTAB TM-599T*	0.05 0.25

*ADVASTAB is a registered trademark of Morton International, Inc.

**includes minor amounts of compounds of Formulas 3-7

Table XV

PVC Color Hold (Yellowness Index) During Processing by Two-Roll Mill @ 390°F											
min/ex	1	2	3	4	5	6	7	8	9	10	11
CE 3	6.7	8.2	9.1	10.2	12.0	14.5	18.2	22.3	25.2	26.0	29.4
CE 4	4.6	5.6	6.8	8.8	12.2	16.0	19.8	23.4	24.6	27.3	29.5
21	4.0	4.1	4.6	5.7	7.2	11.4	14.0	17.9	20.8	23.3	26.4

Table XV (continued)

PVC Color Hold (Yellowness Index) During Processing by Two-Roll Mill @ 390°F											
min/ex	1	2	3	4	5	6	7	8	9	10	11
22	5.1	6.2	6.3	7.0	8.2	11.4	15.1	19.1	21.0	24.0	26.5

Example 23

Preparation of Intermediate

[0067] A mixture of 736.16 grams (8 moles) of thioglycolic acid, 848.96 grams (8 moles) of diethyleneglycol, and 1.3 grams of p-toluene sulfonic acid was heated to 80°C at a pressure of 400 Torr in a reactor equipped with a mechanical stirrer, a thermometer, and a vacuum take-off condenser. The refluxing temperature was held for 1 hour before the pressure was reduced to 120 Torr over a period of 2.5 hours to remove water formed by the esterification. The temperature rose to 120°C as the pressure was further reduced to 20 Torr over a period of 0.5 hour. The total weight of water removed was 140.92 grams. The product has an acid value of 12 and an SH content of 16.75% by weight. The yield was 1421.12 grams. The product was a mixture of the diethyleneglycol mono- and diesters of thioglycolic acid (i. e., hydroxyethyloxyethylmercaptoacetate and ethyloxyethyl dimercaptoacetate) and was satisfactory.

Preparation of Adduct

[0068] To the 1421 grams (7.89 equivalents) of intermediate thus produced there was added 6.38 grams of AMBERLYST 15 ion exchange resin and then 708.21 grams (8.42 equivalents) of 3,4-dihydro(2H)pyran (DHP) was added dropwise over a period of 135 minutes under a nitrogen blanket at a temperature 40-50°C. After continued heating at 40-50°C for 2.25 hours, the %SH was 5.36. Another charge of DHP weighing 300.21 grams (about 3.5 moles) was added during a period of 0.5 hour and the reaction mixture was held at about 55°C for 0.5 hour to reduce the %SH to 3,32. After standing overnight (about 14 hours) under nitrogen, the product had an SH content of 2.68 %.

[0069] The product was a mixture containing 2-S-(tetrahydropyranyl) hydroxyethyloxyethylthioglycolate, wherein R^1 is hydroxyethoxyethoxyacetylmethyl, and bis-[2-S-(tetrahydropyranyl)ethyloxyethyl] thioglycolate, wherein y is 2 and R^1 is oxy[bis(ethoxyacetylmethyl)].

Example 24

Preparation of intermediate

[0070] A mixture of 98.23 grams (1.07 moles) of thioglycolic acid, 160.06 grams (1.07 moles) of triethyleneglycol, and 0.2 gram of p-toluene sulfonic acid was heated to 100°C at a pressure of 250 Torr in a reactor equipped with a mechanical stirrer, a thermometer, and a vacuum take-off condenser. The refluxing temperature was held for 25 minutes before the pressure was reduced to 10 Torr over a period of 1.5 hours to remove water formed by the esterification. The product contained the triethyleneglycol monoester (about 57% of the total weight) and the triethyleneglycol diester of thioglycolic acid (about 20 %) and was satisfactory.

Preparation of Adduct

[0071] A mixture containing (2-S-tetrahydropyranyl) hydroxyethyloxyethyloxyethylthioglycolate and bis-(2-S-tetrahydropyranyl)ethyloxyethyloxyethyl di-thioglycolate was prepared by cooling 100 grams (0.42 equivalent of SH) of the thus prepared mixture of triethyleneglycol mono- and diesters of thioglycolic acid along with 0.2 gram of AMBERLYST 15 ion exchange resin to 0°C and adding 39.18 grams (0.462 mole) of DHP dropwise over a period of 30 minutes. The mixture was held at 0°C for 1 hour and then heated gradually to room temperature (about 22°C) and held there for 2 hours. The yield of product was 139.2 grams and the SH content was 3.5%.

Example 25

Preparation of Intermediate

[0072] A mixture of 92.0 grams (1 mole) of thioglycolic acid, 212.21 grams (2 moles) of diethyleneglycol, and 0.24 gram of p-toluene sulfonic acid was heated to 100°C at a pressure of 200 Torr in a reactor equipped with a mechanical

stirrer, a thermometer, and a vacuum take-off condenser. The temperature was held for 0.5 hour before the pressure was reduced to 10 Torr over a period of 1.9 hours and then held for 70 minutes to remove water formed by the esterification. The temperature was raised to 110°C as the pressure was further reduced to less than 1 Torr over a period and held for 3 hours. The diethyleneglycol monoester of thioglycolic acid constituted 85.9 % and the diester constituted 14.1 % of the weight of the product. The SH content of the product was 19.49% by weight, which was satisfactory.

Preparation of Adduct

[0073] A mixture of 70 grams (0.412 equivalent) of the intermediate thus produced and 0.15 gram of AMBERLYST 15 ion exchange resin was cooled to less than 0.5°C and then 36.52 grams (0.434 equivalent) of DHP was added dropwise over a period of about 7 minutes and after 3 hours it was warmed to room temperature (about 22°C).

Examples 26-28 and Comparative Examples 5 & 6

[0074] A conventional rigid PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=65)	100.0 parts
Calcium carbonate	5.00 phr
Titanium dioxide	1.0 phr
Calcium stearate	0.6* phr
Paraffin wax	1.2 phr
Oxidized polyethylene	0.15 phr

* 0.45 in Comp. Ex. 4 and Ex. 28

was modified as shown in Table XVI and the resulting compositions were processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 390°F with chips taken at one minute intervals to a maximum of 12 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the dE was selected as the measurement for comparison in Table XVII. The DTS, measured as described above but at 190°C, is shown in Table XVIII.

Table XVI

Stabilizer Systems Evaluated		
Reference phr	Stabilizer	Use Level,
Comp. Ex. 5	ADVASTAB TM-599 stabilizer	0.45*
Comp. Ex. 6	ADVASTAB LS-203 lube & stabilizer **	2.40
26	Product of Example 22 Zinc octoate (18% zinc)l	0.70 0.13
27	Product of Example 23 Zinc octoate (18% zinc)	0.70 0.13
28	Product of Example 24 Zinc octoate (18% zinc)	0.70 0.13

* Higher than normal amount for PVC pipe

** TM-599 plus lubricant

Table XVII

PVC Color Hold (dE) During Processing by Two-Roll Mill @ 390°F												
min/ex	1	2	3	4	5	6	7	8	9	10	11	12
CE 5	15.8	15.8	16.1	15.8	16.0	15.9	16.8	17.2	17.9	18.5	20.0	21.2
26	16.7	16.2	15.7	16.1	15.8	16.9	17.5	18.6	21.4	27.0	36.2	43.2

Table XVII (continued)

PVC Color Hold (dE) During Processing by Two-Roll Mill @ 390°F												
min/ex	1	2	3	4	5	6	7	8	9	10	11	12
27	16.0	15.4	15.5	15.4	16.1	16.5	18.3	24.4	28.6	40.8	46.8	48.8
CE 6	11.5	11.7	12.3	13.0	12.1	13.2	14.5	14.7	15.4	16.7	18.8	19.9
28	12.3	11.5	12.1	12.7	12.2	14.3	15.7	20.5	28.9	35.9	41.5	42.8

Table XVIII

PVC Dynamic Thermal Stability by Brabender @190°C	
	Minutes
Comparative Example 5	9.6
26	9.9
27	8.6
Comparative Example 6	13.9
28	9.9

Example 29 and Comparative Example 7

[0075] The following examples compare the thermal stability of a semi-rigid PVC composition containing a homogeneous blend of zinc chloride and the latent mercaptan of this invention (Formula 2 along with the by-products shown by Formulas 3-7) with that of a semi-rigid PVC composition containing a commercial Cd/Ba/Zn/phosphite stabilizer.

[0076] The homogeneous blend of zinc chloride and the latent mercaptan was prepared by charging dropwise a solution of 16.0 grams of anhydrous zinc chloride in 50 mls of dry acetone into 333.2 grams of the latent mercaptan with stirring at 30°C under a nitrogen blanket and then removing the acetone by heating the solution at 55°C for one hour under a reduced pressure of 15 mm Hg. Filtration of the remaining liquid yielded a sparkling clear homogeneous product having a zinc content of 2.1% by weight.

[0077] A conventional semi-rigid PVC composition containing:

INGREDIENT	AMOUNT
PVC resin (k=70)	100.0 parts
Diisodecyl phthalate	27.0
Epoxidized soybean oil	3.0
Calcium carbonate	30.0 phr
Stearic acid	0.5 phr

was modified as shown in Table XIX and the resulting compositions were processed on a standard horizontal two-roll mill (roll speeds 30R/40R) at 350°F with chips taken at five minute intervals to a maximum of 60 minutes. The color properties of the chips were measured using a Hunter Labs Colorimeter (L, a, b) and the yellowness index was selected as the measurement for comparison in Table XX.

Table XIX

Stabilizer Systems Evaluated		
Example	Stabilizer	Use Level, phr
30	Product of Example 29	2.25
Comp. Ex. 7	Liquid Cd/Ba/Zn/phosphite Solid Ba/Zn booster	3.00 0.50

Table XX

PVC Color Hold (YI) During Processing by Two-Roll Mill @ 350°F												
min/ex	5	10	15	20	25	30	35	40	45	50	55	60
30	14.8	16.9	18.8	20.2	21.4	22.7	24.8	27.3	31.3	35.6	39.4	45.3
CE 7	16.7	21.1	25.2	28.5	31.7	34.0	36.4	38.6	41.4	44.2	46.0	48.3

[0078] The DTS, recorded as the point at which a sharp upturn in the torque rheometry curve occurs at 200°C on a BRABENDER PL-2000 rheometer having an electric head and No. 6 roller blades, is shown in Table XXI.

Table XXI

PVC Dynamic Thermal Stability by Brabender @200°C, 80 rpm	
30	25.4 minutes
Comparative Example 7	26.5 minutes

[0079] The preferred ratio of zinc to sulfur, as they occur in the various combinations of zinc carboxylate or zinc chloride with the latent mercaptan of this invention to make a stabilizer for certain applications of the flexible PVC compositions of this invention, is as shown in Table XXII:

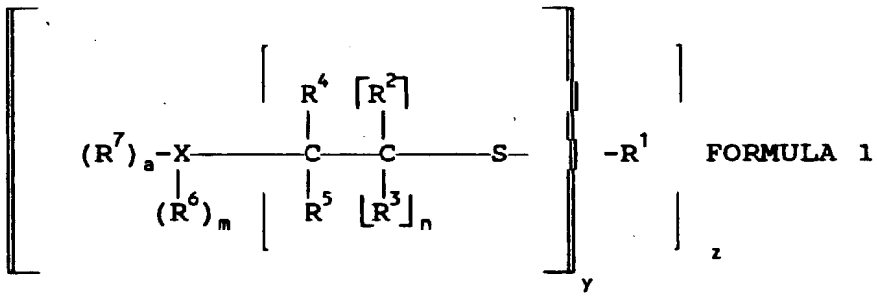
TABLE XXII

APPLICATION	% Filler	Zn:S Ratio	% Zn in stabilizer
Clear calender and extrusion	0.0	0.06:1	0.4
Low fill calender and extrusion; W+C	≤ 10	0.12:1	0.9
Mod. filled calender and extrusion; awning	10-25	0.18:1	1.3
Mbd. filled calender and extrusion	10-25	0.24:1	1.7
High filled calender and extrusion	25.0	0.32:1	2.2
Filled plastisol	N/A	0.60:1	3.6

[0080] Articles of manufacture contemplated by this invention, e.g. packaging film, tubing, rigid pipe, and window profile, are formed from the stabilized compositions of this invention by any of the well-known conventional techniques for forming polymers into shaped articles.

Claims

1. A polymer composition comprising a halogen-containing polymer and degradation products of a blocked mercaptan present during processing of the composition at an elevated temperature, said blocked mercaptan having the structure:



FORMULA 1

wherein a is 1, m is 0, n is 0 or 1; y is 1 or 2, and z is 1; R^1 is a hydroxyalkyl, hydroxy(polyalkoxy) alkyl, hydroxy (polyalkoxy)acylalkyl, acyloxyalkyl, acyloxy(hydroxyalkyl), acyloxy(alkoxyalkyl), acyloxy(polyalkoxy)alkyl, acyloxy (polyalkoxy)acylalkyl, oxy[bis(alkoxyacylalkyl)], oxy[bis(polyalkoxyacylalkyl)], benzoyloxy(polyalkoxy)alkyl, benzoyloxy(polyalkoxy)acylalkyl, or alkylene bis-(acyloxyalkyl) group in which the alkyl moieties have from 2 to 20 carbon atoms, the acyloxy moieties have from 2 to 22 carbon atoms; either R^3 or R^5 is joined with R^7 and 0 to form a heterocyclic moiety, and the rest of R^2, R^3, R^4, and R^5 are hydrogen; and between 0.005% and 0.5%, based on the weight of the polymer, of a synergist comprising a metallic-based heat stabilizer, a Lewis acid or a mixture thereof.

2. A composition according to claim 1 wherein the halogen-containing polymer is a flexible PVC composition and R^1 is an acyloxyalkyl group.

3. A composition according to claim 1 wherein the halogen-containing polymer is a rigid PVC and R^1 is a hydroxy (polyalkoxy)acylalkyl group.

4. A composition according to claim 1 wherein the halogen-containing polymer is a rigid PVC and R^1 is a hydroxyalkyl group.

5. A composition according to any preceding claim wherein the synergist is a metallic-based stabilizer.

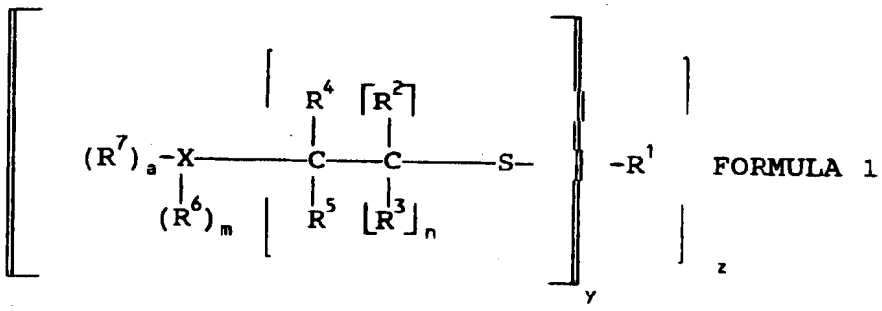
6. A composition according to any one of claims 1 to 4 wherein the synergist is a Lewis acid.

7. A composition according to any preceding claim wherein the metallic-based stabilizer is a zinc carboxylate.

8. A composition according to any preceding claim wherein the Lewis acid is zinc chloride.

9. A composition according to any preceding claim wherein the alkyl moieties of Formula 1 are ethyl.

10. A stabilizer composition comprising from 87.5% to 98.5%, by weight, of a blocked mercaptan having the structure:



FORMULA 1

wherein a is 1, m is 0, n is 0 or 1; y is 1 or 2, and z is 1; R^1 is a hydroxyalkyl, hydroxy(polyalkoxy)alkyl, hydroxy (polyalkoxy)acylalkyl, acyloxyalkyl, acyloxy(hydroxyalkyl), acyloxy(alkoxyalkyl), acyloxy(polyalkoxy)alkyl, acyloxy (polyalkoxy)acylalkyl, oxy[bis(alkoxyacylalkyl)], oxy[bis(polyalkoxyacylalkyl], benzoyloxy(polyalkoxy)alkyl, benzoyloxy(polyalkoxy)acylalkyl, or alkylene bis-(acyloxyalkyl) group in which the alkyl moieties have from 2 to 20 carbon atoms, the acyloxy moieties have from 2 to 22 carbon atoms; R^2, R^3, R^4, and R^5 are hydrogen; and either R^3 or R^5 is joined with R^7 and O to form a heterocyclic moiety;

the balance comprising a synergist which is a metal-based stabilizer, a Lewis acid or a mixture thereof.

11. A composition according to claim 10 wherein the metallic-based heat stabilizer is an organometal compound.

12. A composition according to claim 11 wherein the metallic-based heat stabilizer is a zinc carboxylate.

13. A composition according to any one of claims 10 to 12 wherein the synergist comprises a Lewis acid.

14. A composition according to claim 13 wherein the Lewis acid is zinc chloride.

15. A composition according to any one of claims 10 to 14 wherein the blocked mercaptan constitutes from 93.5% to 97.5% of the total weight.

16. A composition according to any one of claims 10 to 15 characterised further in that it is a clear, homogenous liquid.

17. A composition according to any one of claims 10 to 16 wherein the alkyl moieties of Formula 1 are ethyl.

18. A method for the preparation of a composition for stabilizing a halogen-containing polymer, said method comprising reacting acrolein with a vinyl ether in the presence of a catalytic amount of zinc chloride to form a 3,4-dihydro-2-substituted-2H-pyran and reacting said pyran with a mercaptan whereby the sulfhydryl group of the mercaptan adds across the double bond of the pyran to form a latent mercaptan in admixture with the zinc chloride.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 2322

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 224 679 A (HUELS CHEMISCHE WERKE AG) 10 June 1987 * page 6, column 30 - page 8, column 30 *	1,2,5,7, 9-12	C08K13/02 C08L27/06 //(C08K13/02, 3:16,5:098, 5:37)
A	* page 6, column 5 - column 30 *	18	
A	EP 0 260 380 A (ARGUS CHEM) 23 March 1988 * examples 13-20; tables D,E *	1-18	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C08K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 June 1999	Friederich, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 30 2322

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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29-06-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 62146942 A	30-06-1987
		US 4973619 A	27-11-1990
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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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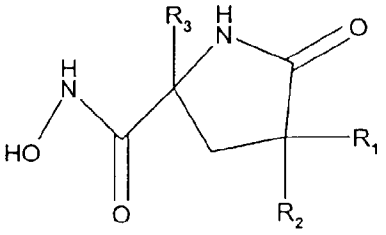
(54) 5-oxo-pyrrolidine-2-carboxylic acid hydroxamide derivatives

(57) The present invention relates to a compound of the formula



wherein R^1, R^2, R^3 are as defined above, to pharmaceutical compositions and methods of treatment.

EP 1 004 578 A2

Description

Background of the Invention

[0001] The present invention relates to 5-oxo-pyrrolidine-2-carboxylic acid hydroxamide derivatives, and to pharmaceutical compositions and methods of treatment.

[0002] The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and reprolysin (also known as adamylsin) subfamilies of the metzincins (Rawlings, et al., Methods in Enzymology, 248, 183-228 (1995) and Stocker, et al., Protein Science, 4, 823-840 (1995)).

[0003] The MMP subfamily of enzymes, currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMP's are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation. In addition, the MMP's are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13, an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, et al., J. Clin. Invest., 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMP's is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

[0004] The mammalian reprolysins are known as ADAMs (A Disintegrin And Metalloproteinase) (Wolfberg, et al., J. Cell Biol., 131, 275-278 (1995)) and contain a disintegrin domain in addition to a metalloproteinase-like domain. To date, twenty three distinct ADAM's have been identified.

[0005] ADAM-17, also known as tumor necrosis factor-alpha converting enzyme (TACE), is the most well known ADAM. ADAM-17 (TACE) is responsible for cleavage of cell bound tumor necrosis factor-alpha (TNF-α, also known as cachectin). TNF-α is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 285, 199 (1991)). Furthermore, it has been shown that TNF-α is the prime mediator of the inflammatory response seen in sepsis and septic shock (Spooner, et al., Clinical Immunology and Immunopathology, 62 S11 (1992)). There are two forms of TNF-α, a type II membrane protein of relative molecular mass 26,000 (26 kD) and a soluble 17 kD form generated from the cell bound protein by specific proteolytic cleavage. The soluble 17 kD form of TNF-α is released by the cell and is associated with the deleterious effects of TNF-α. This form of TNF-α is also capable of acting at sites distant from the site of synthesis. Thus, inhibitors of TACE prevent the formation of soluble TNF-α and prevent the deleterious effects of the soluble factor.

[0006] Select compounds of the invention are potent inhibitors of aggrecanase, an enzyme important in the degradation of cartilage aggrecan. Aggrecanase is also believed to be an ADAM. The loss of aggrecan from the cartilage matrix is an important factor in the progression of joint diseases such as osteoarthritis and rheumatoid arthritis and inhibition of aggrecanase is expected to slow or block the loss of cartilage in these diseases.

[0007] Other ADAMs that have shown expression in pathological situations include ADAM TS-1 (Kuno, et al., J. Biol. Chem., 272, 556-562 (1997)), and ADAM's 10, 12 and 15 (Wu, et al., Biochem. Biophys. Res. Comm., 235, 437-442, (1997)). As knowledge of the expression, physiological substrates and disease association of the ADAM's increases the full significance of the role of inhibition of this class of enzymes will be appreciated.

[0008] Diseases in which inhibition of MMP's and or ADAM's will provide therapeutic benefit include: arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase or ADAM expression.

[0009] This invention also relates to a method of using the compounds of the invention in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefore.

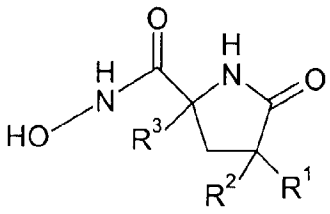
[0010] It is recognized that different combinations of MMP's and ADAM's are expressed in different pathological situations. As such, inhibitors with specific selectivities for individual ADAM's and/or MMP's may be preferred for individual diseases. For example, rheumatoid arthritis is an inflammatory joint disease characterized by excessive TNF

levels and the loss of joint matrix constituents. In this case, a compound that inhibits TACE and aggrecanase as well as MMP's such as MMP-13 may be the preferred therapy. In contrast, in a less inflammatory joint disease such as osteoarthritis, compounds that inhibit matrix degrading MMP's such as MMP-13 but not TACE may be preferred.

[0011] The present inventors have also discovered that it is possible to design inhibitors with differential metalloprotease activity. Specifically, for example, the inventors have been able to design molecules which selectively inhibit matrix metalloprotease-13 (MMP-13) preferentially over MMP-1.

Summary of the Invention

[0012] The present invention relates to compounds of the formula



I

wherein R^1 is $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy $(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$ heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, wherein each of said $(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl moieties is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring, independently selected from fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy; and

R^2 and R^3 are independently selected from H, $(C_1\text{-}C_6)$alkyl, and $CH_2(C_6\text{-}C_{10})$aryl;

and the pharmaceutically acceptable salts thereof.

[0013] Preferred compounds of the present invention relate to compounds wherein R^1 is $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$ alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, or $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, wherein each $(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl moieties of said $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$ aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$ heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl or $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring (preferably one to three substituents, most preferably 0-2 substituents) independently selected from fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy.

[0014] In another embodiment, R^2 and R^3 are hydrogen. In a further embodiment, one or both of R^2 and R^3 are independently selected from $(C_1\text{-}C_6)$alkyl, and $CH_2(C_6\text{-}C_{10})$aryl.

[0015] The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

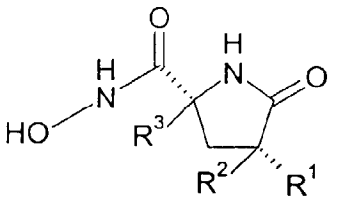
[0016] The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is as defined above.

[0017] The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, bromo, perfluoro$(C_1\text{-}C_6)$alkyl (including trifluoromethyl), $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryloxy, perfluoro$(C_1\text{-}C_3)$alkoxy (including trifluoromethoxy and difluoromethoxy) and $(C_1\text{-}C_6)$alkyl.

[0018] The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl. Preferred heteroaryls include pyridyl, furyl, thienyl, isothiazolyl, pyrazinyl, pyrimidyl, pyrazolyl, isoxazolyl, thiazolyl or oxazolyl. Most preferred heteroaryls include pyridyl, furyl or thienyl.

[0019] The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, tautomers and stereoisomers of the compounds of formula I and mixtures thereof.

[0020] More preferred compounds of the present invention relate to a compound of formula I with the stereochemistry



I'

[0021] More preferred compounds of the present invention relate to a compound of formula I, wherein R^1 is optionally substituted (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy (C_6-C_{10})aryl, preferably substituted with one to three substituents (most preferably zero or one substituent) independently selected from hydrogen, fluoro, chloro, (C_1-C_6)alkyl or (C_1-C_6)alkoxy. When the compound of formula I possesses a substituent, that substituent is most preferably in the para or ortho position of the terminal ring.

[0022] Specific preferred compounds of formula I are selected from the group consisting of:

(2*R*, 4*S*)-4-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide, and
(2*R*, 4*S*)-4-[4-(4-fluorophenoxy)phenyl]-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide.

[0023] Other compounds of formula I are selected from the group consisting of:

(2*R*, 4*S*)-5-oxo-4-(4-phenoxyphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-chlorophenoxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[3-(4-chlorophenoxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[3-(4-fluorophenoxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-5-oxo-4-[4-(pyridin-4-yloxy)-phenyl]pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-biphenyl-4-yl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4'-fluorobiphenyl-4-yl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4-benzyloxyphenyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-5-oxo-4-(4-phenethylphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-fluorobenzyloxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(3,5-difluorobenzyloxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4-methoxybenzyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4'-fluorobiphenyl-4-ylmethyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-naphthalen-2-yl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-fluorophenoxy)-phenyl]-2,4-dimethyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-fluorophenoxy)-phenyl]-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*R*)-4-benzyl-5-oxo-4-(4-phenoxyphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-chlorophenoxy)phenyl]-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide, and
(2*R*, 4*S*)-4-[4-(4-chlorophenoxy)phenyl]-2,4-dimethyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide.

[0024] The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate,

phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

[0025] The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or watersoluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

[0026] The present invention also relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, bums, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase activity and other diseases characterized by mammalian reprolysin activity in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

[0027] The present invention also relates to a pharmaceutical composition for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, most preferably ADAM-17) in a mammal, including a human, comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0028] The present invention also relates to a method for treating a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, bums, diabetes, tumor invasion, tumor growth, tumor metastasis, comeal scarring, scleritis, AIDS, sepsis, septic shock and other diseases characterized by metalloproteinase activity and other diseases characterized by mammalian reprolysin activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

[0029] The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or other metalloproteinases involved in matrix degradation, or (b) a mammalian reprolysin (such as aggrecanase or ADAM's TS-1, 10, 12, 15 and 17, preferably ADAM-17) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0030] This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprolysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, omithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

[0031] One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

[0032] For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicilamine, auranofin or parenteral or oral gold.

[0033] The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

[0034] The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, and antimetabolites such as methotrexate.

[0035] The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

[0036] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, requip, miratex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as Aricept, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

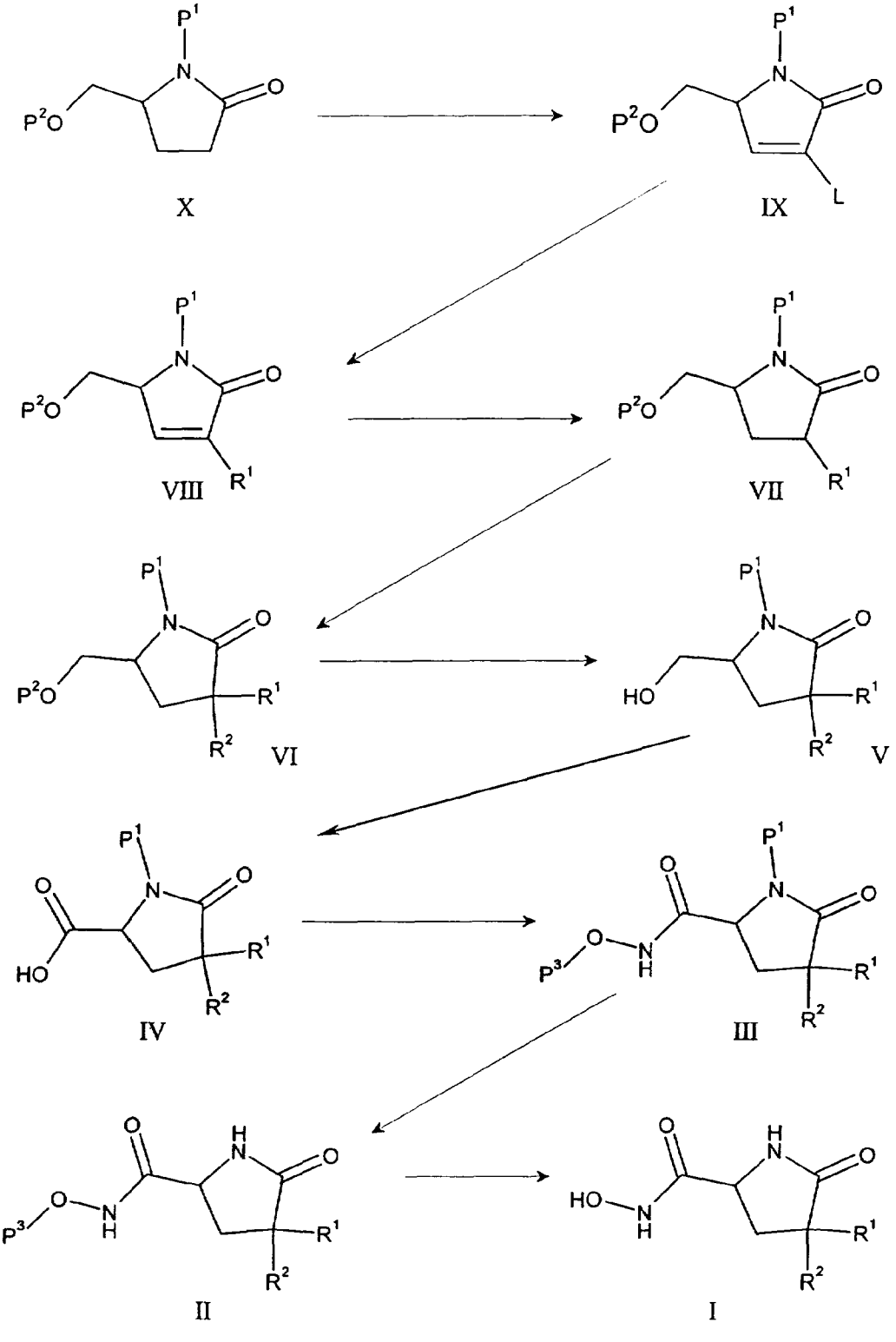
[0037] The compounds of the present invention may also be used in combination with osteoporosis agents such as droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

Detailed Description of the Invention

[0038] The following reaction schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated, R^1, R^2, and R^3 in the reaction schemes and the discussion that follows are defined as above.

[0039] Reaction scheme 1 shows the synthesis of compounds where R^2 is hydrogen, $(C_1\text{-}C_6)$ alkyl or $CH_2(C_6\text{-}C_{10})$ aryl and R^3 is hydrogen.

Scheme 1



[0040] Referring to Scheme 1, compounds of the formula I are prepared from hydroxamic acid derivatives of the formula II by removal of the hydroxy amide protecting group P^3. When P^3 is benzyl, removal of the hydroxy amide

protecting group is carried out by hydrogenolysis using catalytic palladium on barium sulfate in a polar solvent at a temperature from about 20°C to about 25°C, i.e. room temperature, for a period of about 1 hour to about 5 hours, preferably about 3 hours. When P^3 is other than benzyl, removal is facilitated such as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (Willey Interscience, 2nd Ed.) (1991), Chapter 2.

[0041] The compound of formula II is prepared from a compound of formula III by removal of the P^1 protecting group, wherein P^1 is as defined below. When P^1 is a t-butoxy carbonyl protecting group, removal is effected by using an acid in an inert solvent. When P^1 is other than t-butoxy carbonyl, removal is as described in Greene and Wuts, id. at p. 397-405. Suitable acids include hydrochloric and trifluoroacetic acid, preferably hydrochloric acid. Suitable solvents include methylene chloride, diethyl ether, or chloroform, preferably methylene chloride. The reaction is carried out at a temperature ranging from about -25°C to 50°C; preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is conducted over a period of about 15 minutes to about 2 hours, preferably about 30 minutes.

[0042] The hydroxamic acid derivative of formula III is prepared from a carboxylic acid compound of formula IV by reaction with a suitably protected hydroxylamine derivative of the formula P^3-ONH_2, wherein P^3 is as defined in Greene and Wuts, id., and (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, at room temperature, in a polar solvent. Suitable bases include triethylamine, N-methylmorpholine or diisopropylethylamine, preferably diisopropylethylamine. Suitable solvents include THF, methylene chloride, N,N-dimethylformamide or N-methylpyrrolidin-2-one, preferably methylene chloride. Specific P^3 protecting groups include benzyl, t-butyldimethylsilyl, trimethylsilyl, 2-(trimethylsilyl)ethyl or allyl. The aforesaid reaction is conducted for a period of about 2 hours to about 24 hours, preferably about 16 hours. The temperature of the aforesaid reaction varies from about 0°C to about 60°C, preferably about 20°C to about 25°C (room temperature).

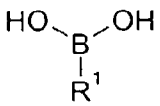
[0043] The carboxylic acid of formula IV is prepared by oxidation of an alcohol of formula V in the presence of periodic acid and catalytic chromium trioxide, in a polar solvent. Suitable solvents include acetonitrile or water, preferably wet acetonitrile (0.75 volume percent water). Suitable temperatures for the aforesaid reaction range from about -10°C to about 25°C, preferably the temperature is about 0°C. The reaction is complete within about 10 minutes to about 24 hours, preferably about 0.5 hours. Alternative oxidation conditions are described in Zhao, et al., Tet. Lett., 39, 5323-5326 (1998).

[0044] The alcohol of formula V is prepared from a compound of formula VI by removal of the protecting groups at P^2, wherein P^2 is as defined below. When P^2 is tert-butyl dimethylsilyl, the reaction is performed by mild hydrolysis in the presence of dilute aqueous mineral acid and a solvent such as diethyl ether. Suitable aqueous mineral acids include dilute hydrochloric acid or sulfuric acid, preferably 0.5 molar hydrochloric acid. The reaction is carried out at a temperature ranging from about 0°C to 50°C; preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is conducted over a period of about 2 hours to about 48 hours, preferably about 16 hours.

[0045] The compound of formula VI, where R^2 is $(C_1$-$C_6)$ alkyl or $CH_2(C_6$-$C_{10})$aryl, is prepared from a compound of formula VII by reacting VII with an alkylating agent of the formula R^2-Z, where Z is bromo or iodo, and strong base such as lithium diisopropylamide or lithium (bis)trimethylsilylamide (preferably lithium diisopropylamide) in an inert solvent such as diethyl ether or tetrahydrofuran (preferably tetrahydrofuran). The reaction is carried out at a temperature of from -78°C to 0°C, preferably -78°C for a period of from 1 to 24 hours, preferably about 16 hours.

[0046] The compound of formula VII is prepared from a compound of formula VIII by hydrogenation under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include palladium on barium sulfate, palladium on carbon, palladium hydroxide on carbon or carbon black. The preferred catalyst is palladium hydroxide on carbon. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours. Alternatively, the reduction can be performed using dissolving metal conditions or by using L-selectride.

[0047] The compound of formula VIII can be prepared from a compound of the formula IX by Suzuki coupling, preferably by reaction with a boronic acid of the formula



in the presence of a catalyst and a base in a suitable solvent. Suitable catalysts include palladium (II) acetate, tetrakis (triphenylphosphene)palladium and tetrakis[tris-(2-methoxyphenyl)-phosphine]palladium, preferably tetrakis(triphenyl-

phosphene)palladium. Suitable bases include aqueous sodium carbonate, aqueous potassium carbonate, or aqueous cesium carbonate, preferably aqueous sodium carbonate. Suitable solvents include ethers, toluene, and hexane, preferably toluene. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 110°C, preferably the temperature may range from about 75°C to about 110°C. The reaction is complete within about 0.5 hours to about 24 hours, preferably about 16 hours. Suzuki couplings are well known to those of ordinary skill in the art such as described in Suzuki, Pure Appl. Chem., 63, 419-422 (1991), Tetrahedron, 263 (1997) and Chem. Rev., 95, 2457-2483 (1995). Boronic acids can also be prepared by methods well known to those of ordinary skill in the art, such as those described in Caron, et al., JOC, 63, 2054-2055 (1998).

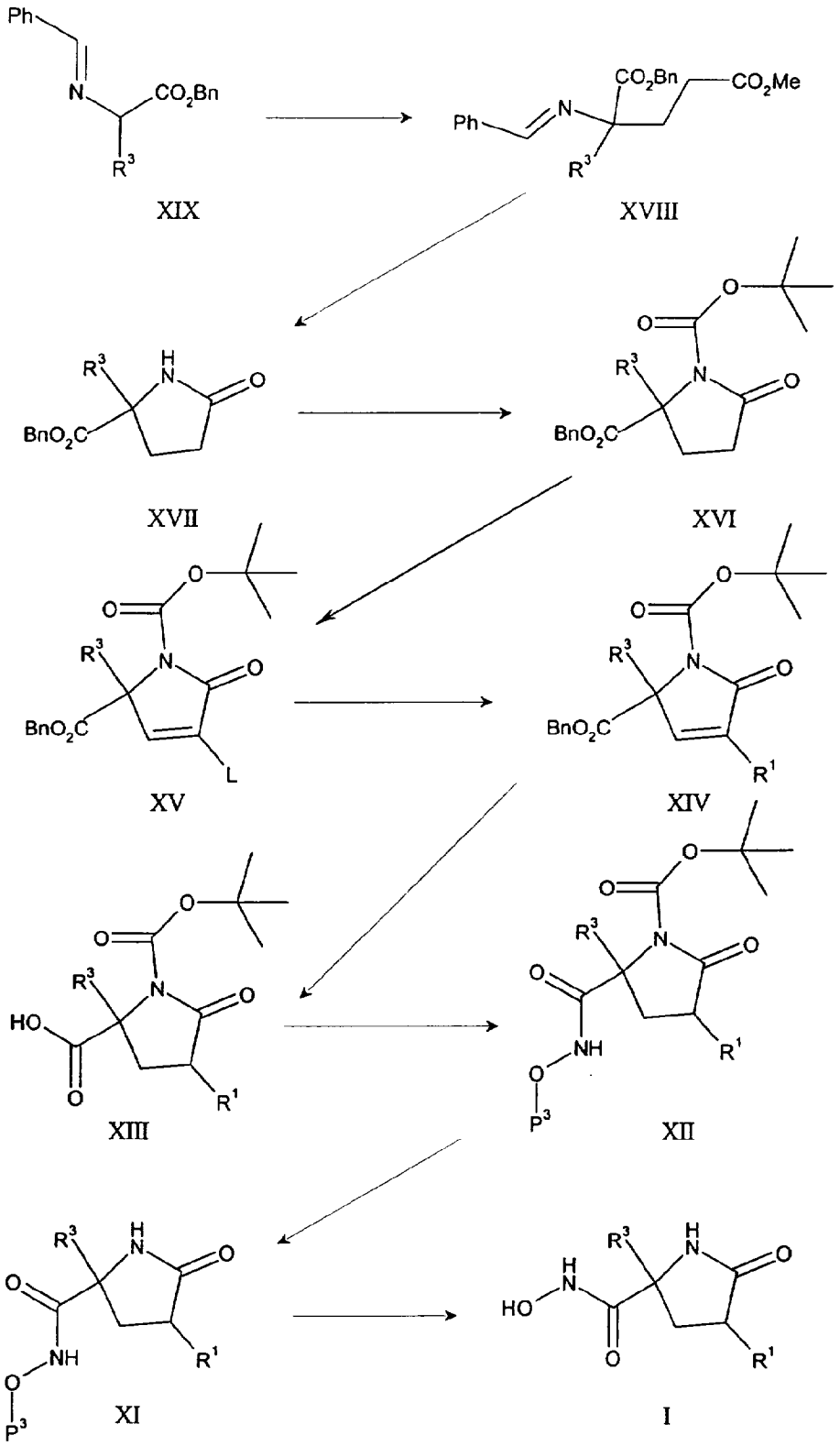
[0048] Compounds of the formula VIII can also be prepared from compounds of the formula IX by reaction with organometallic reagents of the formula R^1-M, wherein M is magnesium, lithium, tin, zinc, copper, or boron, in the presence of an appropriate transition metal catalyst such as catalysts based on palladium or nickel.

[0049] The compound of formula IX, wherein L is bromo or iodo, can be prepared from a compound of formula X by reaction with a base, phenylselenenylbromide and a halogenating agent followed by oxidation in the presence of hydrogen peroxide. Suitable bases include lithium bis(trimethylsilyl)amide or lithium diisopropylamide, preferably lithium bis(trimethylsilyl)amide. Suitable halogenating agents include 1,2-dibromotetrachloroethane or N-iodosuccinamide, preferably 1,2-dibromotetrachloroethane. Suitable temperatures for the aforesaid reaction range from about -78°C to about -30°C, preferably the temperature is about -78°C. The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours. The oxidation step is performed at a temperature of about 0°C to about 50°C, preferably at about room temperature. The aforesaid oxidation step is complete within about 2 hours to about 24 hours, preferably about 16 hours. Suitable solvents for the oxidation step include methylene chloride. Other conditions for the aforesaid reaction are described in Fray, et al., JOC, 61, 3362-3374 (1996).

[0050] Compounds of the formula X, wherein P^1 and P^2 are protective groups as described in Greene and Wuts, supra, are known or can be made by methods well known to those of ordinary skill in the art. One example of a method of preparation of a compound of formula X, wherein P^1 is tertbutoxy carbonyl and P^2 is t-butyldimethylsilyl, is described in Yoda et al., Tetrahedron, 7(7), 2113-2116 (1996). Suitable P^1 protecting groups include tert-butoxycarbonyl, benzyloxycarbonyl, methoxycarbonyl, 2-(trimethylsilyl)ethyloxycarbonyl, trifluoroacetyl or 2,2,2-trichloroethoxycarbonyl. Suitable P^2 protecting groups include t-butyldiphenylsilyl, benzyl, methoxymethyl(MOM) or tetrahydropyranyl.

[0051] Scheme 2 shows the synthesis of compounds where R^2 is hydrogen and R^3 is (C_1-C_6) alkyl or CH_2(C_6-C_{10}) aryl.

Scheme 2


Ph
N
CO2Bn
R3
XIX
CO2Bn
CO2Me
XVIII
BnO2C
XVII
XVI
L
XV
R1
XIV
HO
XIII
NH
P3
XII
XI
I

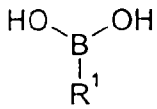
[0052] Referring to Scheme 2, compounds of the formula I are prepared from hydroxamic acid derivatives of the formula XI by removal of the hydroxy amide protecting group P^3. When P^3 is benzyl, removal of the hydroxy amide protecting group is carried out by hydrogenolysis using catalytic palladium on barium sulfate in a polar solvent at a temperature from about 20°C to about 25°C, i.e. room temperature, for a period of about 1 hour to about 5 hours, preferably about 3 hours. When P^3 is other than benzyl, removal is facilitated such as described in Greene and Wuts, supra.

[0053] The compound of formula XI is prepared from a compound of formula XII by treatment with an acid in an inert solvent. Suitable acids include hydrochloric and trifluoroacetic acid, preferably hydrochloric acid. Suitable solvents include methylene chloride, diethyl ether, or chloroform, preferably methylene chloride. The reaction is carried out at a temperature ranging from about -25°C to 50°C; preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is conducted over a period of about 15 minutes to about 2 hours, preferably about 30 minutes.

[0054] The hydroxamic acid derivative of formula XII is prepared from a carboxylic acid compound of formula XIII by reaction with a suitably protected hydroxylamine derivative of the formula P^3-ONH_2, wherein P^3 is as defined in Greene and Wuts, id., and (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, at room temperature, in a polar solvent. Suitable bases include triethylamine, N-methylmorpholine or diisopropylethylamine, preferably diisopropylethylamine. Suitable solvents include THF, methylene chloride, N,N-dimethylformamide or N-methylpyrrolidin-2-one, preferably methylene chloride. Specific P^3 protecting groups include benzyl, t-butyldimethylsilyl, trimethylsilyl, 2-(trimethylsilyl)ethyl or allyl. The aforesaid reaction is conducted for a period of about 2 hours to about 24 hours, preferably about 16 hours. The temperature of the aforesaid reaction varies from about 0°C to about 60°C, preferably about 20°C to about 25°C (room temperature).

[0055] Compounds of formula XIII are prepared from compounds of formula XIV by hydrogenation under an atmosphere of hydrogen in the presence of a catalyst in a reaction inert solvent. Suitable catalysts include palladium on barium sulfate, palladium on carbon, palladium hydroxide on carbon or carbon black. The preferred catalyst is palladium hydroxide on carbon. Suitable solvents include an alcohol such as ethanol, methanol or isopropanol, preferably methanol. The aforesaid reaction may be performed at a pressure from about 1 to about 5 atmospheres, preferably about 3 atmospheres. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours. Alternatively, the reduction can be performed using dissolving metal conditions.

[0056] The compound of formula XIV can be prepared from a compound of the formula XV by Suzuki coupling, preferably by reaction with a boronic acid of the formula



in the presence of a catalyst and a base in a suitable solvent. Suitable catalysts include palladium (II) acetate, tetrakis (triphenylphosphene)palladium and tetrakis[tris-(2-methoxyphenyl)-phosphine]palladium, preferably tetrakis(triphenylphosphene)palladium. Suitable bases include aqueous sodium carbonate, aqueous potassium carbonate, or aqueous cesium carbonate, preferably aqueous sodium carbonate. Suitable solvents include ethers, toluene, and hexane, preferably toluene. Suitable temperatures for the aforesaid reaction range from about 20°C (room temperature) to about 110°C, preferably the temperature may range from about 75°C to about 110°C. The reaction is complete within about 0.5 hours to about 24 hours, preferably about 16 hours.

[0057] Compounds of the formula XIV can also be prepared from compounds of the formula XV by reaction with organometallic reagents of the formula R^1-M, wherein M is magnesium, lithium, tin, zinc, copper, or boron, in the presence of an appropriate transition metal catalyst such as catalysts based on palladium or nickel.

[0058] The compounds of formula XV, wherein L is bromo or iodo, can be prepared from compounds of formula XVI by reaction with a base, phenylselenenylbromide and a halogenating agent followed by oxidation in the presence of hydrogen peroxide. Suitable bases include lithium bis(trimethylsilyl)amide or lithium diisopropylamide, preferably lithium bis(trimethylsilyl)amide. Suitable halogenating agents include 1,2-dibromotetrachloroethane or N-iodosuccinamide, preferably 1,2-dibromotetrachloroethane. Suitable temperatures for the aforesaid reaction range from about -78°C to about -30°C, preferably the temperature is about -78°C. The reaction is complete within about 0.5 hours to about 5 hours, preferably about 3 hours. The oxidation step is performed at a temperature of about 0°C to about 50°C, preferably at about room temperature. The aforesaid oxidation step is complete within about 2 hours to about 24 hours, preferably about 16 hours. Suitable solvents for the oxidation step include methylene chloride. Other conditions for the

aforesaid reaction are described in Fray, et al., supra.

[0059] The compounds of XVI are prepared from compounds of formula XVII by reacting compounds of formula XVII with di-tert-butyl dicarbonate in the presence of a base such as triethylamine or diisopropylethylamine, preferably triethylamine, and a catalytic amount of 4-dimethylaminopyridine in an inert solvent such as methylene chloride, chloroform or tetrahydrofuran, preferably tetrahydrofuran. The reaction is carried out at a temperature of from 0°C to 50°C, preferably about 25°C, for 1 to 48 hours, preferably about 16 hours.

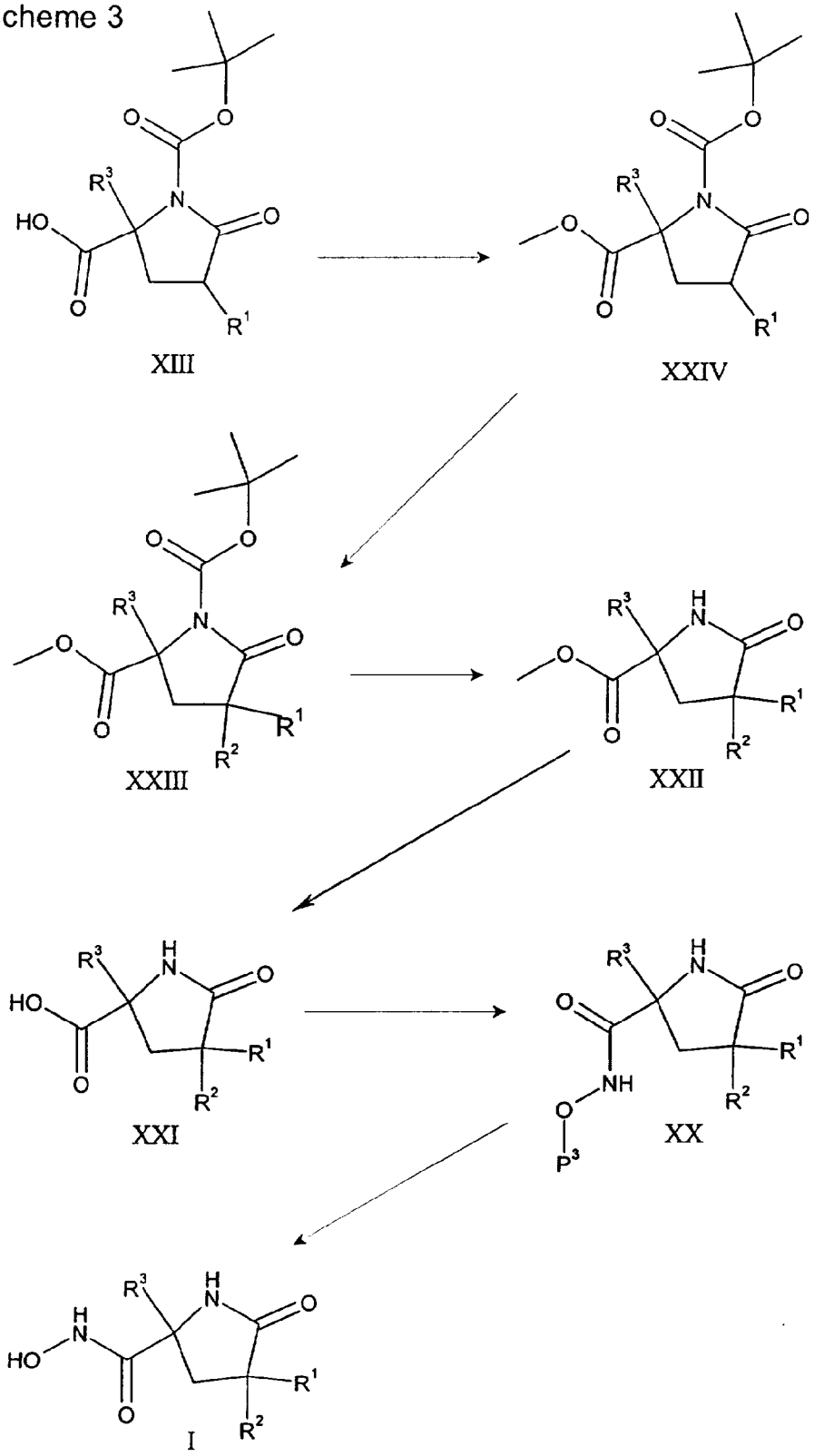
[0060] The compounds of formula XVII are prepared from compounds of formula XVIII by heating the compounds of formula XVIII in water or in a mixture of tetrahydrofuran, methanol and water, constituted such that XVIII is soluble. This reaction is carried out at a temperature of 50°C to 180°C for a period of 1 to 48 hours, preferably about 16 hours.

[0061] The compounds of formula XVIII are prepared from the compounds of XIX by reacting the amino acid derivative of formula XIX with methyl acrylate and a base such as potassium carbonate, cesium carbonate or cesium hydroxide hydrate, preferably potassium carbonate, in the presence of benzyl triethylammonium chloride in a solvent such as acetonitrile or methylene chloride, preferably acetonitrile. The reaction is carried out at a temperature of from 0°C to 50°C, preferably about 25°C for 1 to 24 hours, preferably about 2 hours.

[0062] Compounds of the formula XIX are known or can be made by methods well known to those of ordinary skill in the art.

[0063] Scheme 3 shows the synthesis of compounds of the invention where R^2 and R^3 are independently (C_1-C_6) alkyl or CH_2(C_6-C_{10})aryl.

Scheme 3



[0064] Referring to Scheme 3, compounds of the formula I are prepared from hydroxamic acid derivatives of the formula XX by removal of the hydroxy amide protecting group P^3. When P^3 is benzyl, removal of the hydroxy amide protecting group is carried out by hydrogenolysis using catalytic palladium on barium sulfate in a polar solvent at a temperature from about 20°C to about 25°C, i.e. room temperature, for a period of about 1 hour to about 5 hours, preferably about 3 hours. When P^3 is other than benzyl, removal is facilitated such as described in Greene and Wuts, supra.

[0065] The hydroxamic acid derivatives of formula XX are prepared from carboxylic acid compounds of formula XXI by reaction with a suitably protected hydroxylamine derivative of the formula P^3-ONH_2, wherein P^3 is as defined in Greene and Wuts, *id.,* and (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, at room temperature, in a polar solvent. Suitable bases include triethylamine, N-methylmorpholine or diisopropylethylamine, preferably diisopropylethylamine. Suitable solvents include THF, methylene chloride, N,N-dimethylformamide or N-methylpyrrolidin-2-one, preferably methylene chloride. Specific P^3 protecting groups include benzyl, t-butyldimethylsilyl, trimethylsilyl, 2-(trimethylsilyl)ethyl or allyl. The aforesaid reaction is conducted for a period of about 2 hours to about 24 hours, preferably about 16 hours. The temperature of the aforesaid reaction varies from about 0°C to about 60°C, preferably about 20°C to about 25°C (room temperature).

[0066] The compounds of formula XXI are prepared from compounds of formula XXII by reacting compounds of formula XXII with a base such as lithium hydroxide , sodium hydroxide or potassium hydroxide, preferably lithium hydroxide, in a mixture of water, methanol and tetrahydrofuran (constituted such that XXII is soluble). The reaction is carried out at a reaction temperature of 20°C to 60°C, preferably about 25°C for 1 to 48 hours, preferably about 2 hours.

[0067] Compounds of formula XXII are prepared from compounds of formula XXIII by treatment with an acid in an inert solvent. Suitable acids include hydrochloric and trifluoroacetic acid, preferably hydrochloric acid. Suitable solvents include methylene chloride, diethyl ether, or chloroform, preferably methylene chloride. The reaction is carried out at a temperature ranging from about -25°C to 50°C; preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is conducted over a period of about 15 minutes to about 2 hours, preferably about 30 minutes.

[0068] Compounds of the formula XXIII are prepared from compounds of formula XXIV by reacting XXIV with an alkylating agent of the formula R^2-Z, where Z is bromo or iodo, and strong base such as lithium diisopropylamide or lithium (bis)trimethylsilylamide (preferably lithium diisopropylamide) in an inert solvent such as diethyl ether or tetrahydrofuran (preferably tetrahydrofuran). The reaction is carried out at a temperature of from -78°C to 0°C, preferably -78°C for a period of from 1 to 24 hours, preferably about 16 hours.

[0069] Compounds of formula XXIV are prepared from compounds of formula XIII by reacting compounds of formula XIII with methyl iodide and a base such as sodium carbonate, potassium carbonate or cesium carbonate, preferably cesium carbonate, in an inert solvent such as dimethylformamide or acetone, preferably dimethylformamide. The reaction is conducted at a temperature of 0°C to 50°C, preferably about 25°C. Reaction time: 1 to 48 hours, preferably about 16 hours.

[0070] The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

[0071] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

[0072] Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solu-

tions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

[0073] The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reprolysin and, consequently, demonstrate their effectiveness for treating diseases characterized by metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

[0074] Human recombinant collagenase is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

[0075] Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) are set in wells D1-D6.

[0076] Collagenase-1 is diluted to 240 ng/ml and 25 ml is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

[0077] Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 ml substrate per well of the microfluor plate to give a final concentration of 10 mM.

[0078] Fluorescence readings (360 nM excitation, 460 nm emission) are taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours

[0079] Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

[0080] If IC_{50}'s are reported to be less than 0.03 mM then the inhibitors are assayed at concentrations of 0.3 mM, 0.03 mM, and 0.003 mM.

Inhibition of Gelatinase (MMP-2)

[0081] Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) is activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

[0082] 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM $CaCl_2$, 20 μM $ZnCl_2$ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM---→ 120 μM---→ 12 μM---→ 1.2 μM---→ 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM ---→ 3 μM ---→ 0.3 μM ---→ 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

[0083] Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 pL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.34 nM).

[0084] A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2) is diluted in assay buffer to 20 μM. The assay is initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 10 μM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

[0085] The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on

the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50}'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Stromelysin Activity (MMP-3)

[0086] Human recombinant stromelysin (MMP-3, stromelysin-1) is activated for 20-22 hours with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

[0087] 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM--→ 120 μM---→ 12 μM---→ 1.2 μM---→ 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM ---→ 3 μM ---→ 0.3 μM ---→ 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

[0088] Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 μL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL (0.875 nM).

[0089] A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH_2) is diluted in assay buffer to 6 μM. The assay is initiated by addition of 50 pL of diluted substrate yielding a final assay concentration of 3 μM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

[0090] The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50}'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of MMP-13

[0091] Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 2.0 hours, at 37°C and is diluted to 240 ng/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20mM zinc chloride, 0.02% brij 35). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 60 ng/ml.

[0092] Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase-1 (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 mM, 3mmM, 0.3m mM, and 0.03 mmM.

[0093] Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 nM emission) are taken at time 0 and every 5 minutes for 1 hour.

[0094] Positive controls and negative controls are set up in triplicate as outlined in the MMP-1 assay.

[0095] IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 mM, 0.03 mmM, 0.003 mmM and 0.0003 mM.

Inhibition of TNF Production

[0096] The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

[0097] Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts

determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

[0098] 180 µl of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 µl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFa using the R&D ELISA Kit.

Inhibition of Soluble TNF-α Production

[0099] The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the cellular release of TNF-α and, consequently, demonstrate their effectiveness for treating diseases involving the disregulation of soluble TNF-α is shown by the following in vitro assay:

Method for the evaluation of recombinant TNF-α Converting Enzyme Activity Expression of recombinant TACE

[0100] A DNA fragment coding for the signal sequence, preprodomain, prodomain and catalytic domain of TACE (amino acids 1-473), can be amplified by polymerase chain reaction using a human lung cDNA library as a template. The amplified fragment is then cloned into pFastBac vector. The DNA sequence of the insert is confirmed for both the strands. A bacmid prepared using pFastBac in E. coli DH10Bac is transfected into SF9 insect cells. The virus particles is then amplified to P1, P2, P3 stages. The P3 virus is infected into both Sf9 and High Five insect cells and grown at 27°C for 48 hours. The medium is collected and used for assays and further purification.

Preparation of fluorescent quenched substrate:

[0101] A model peptidic TNF-α substrate (LY-LeucineAlanineGlutamineAlanineValineArgininеSerine-SerineLysine (CTMR)-Arginine (LY=Lucifer Yellow; CTMR=Carboxytetramethyl-Rhodamine)) is prepared and the concentration estimated by absorbance at 560 nm (E_{560}: 60,000 M-1CM-1) according to the method of Geoghegan, KF, "Improved method for converting an unmodified peptide to an energy-transfer substrate for a proteinase." Bioconjugate Chem. **7**, 385-391 (1995). This peptide encompasses the cleavage cite on pro-TNF which is cleaved in vivo by TACE.

Expression of recombinant TACE

[0102] A DNA fragment coding for the signal sequence, preprodomain, prodomain and catalytic domain of TACE (amino acids 1-473), is amplified by polymerase chain reaction using a human lung cDNA library as a template. The amplified fragment is cloned into pFastBac vector. The DNA sequence of the insert is confirmed for both the strands. A bacmid prepared using pFastBac in E. coli DH10Bac is transfected into SF9 insect cells. The virus particles were amplified to P1, P2, P3 stages. The P3 virus is infected into both Sf9 and High Five insect cells and grown at 27°C for 48 hours. The medium is collected and used for assays and further purification.

Enzyme reaction.

[0103] The reaction, carried out in a 96 well plate (Dynatech), is comprised of 70 µl of buffer solution (25 mM Hepes-HCl, pH7.5, plus 20 uM $ZnCl_2$), 10 µl of 100 µM fluorescent quenched substrate, 10 µl of a DMSO (5%) solution of test compound, and an amount of r-TACE enzyme which will cause 50% cleavage in 60 minutes - in a total volume of 100 µl. The specificity of the enzyme cleavage at the amide bond between alanine and valine is verified by HPLC and mass spectrometry. Initial rates of cleavage are monitored by measuring the rate of increase in fluorescence at 530 nm (excitation at 409 nm) over 30 minutes. The experiment is controlled as follows: 1) for background fluorescence of substrate; 2) for fluorescence of fully cleaved substrate; 3) for fluorescence quenching or augmentation from solutions containing test compound.

[0104] Data is analyzed as follows. The rates from the non-test compound containing "control" reactions were averaged to establish the 100% value. The rate of reaction in the presence of test compound was compared to that in the absence of compound, and tabulated as "percent of non-test compound containing control. The results are plotted as "% of control" vs. the log of compound concentration and a half-maximal point or IC_{50} value determined.

[0105] All of the compounds of the invention have IC_{50} of less than 1 pM, preferably less than 50nM. Most preferred compounds of the invention are at least 100 fold less potent against r-MMP-1 than in the above TACE assay.

Human Monocyte Assay

[0106] Human mononuclear cells are isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells are washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2×10^6/ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

[0107] 180m of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 µl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF-α using the R&D ELISA Kit.

Aggrecanase Assay

[0108] Primary porcine chondrocytes from articular joint cartilage are isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at 2×10^5 cells per well into 48 well plates with 5 µCi / ml ^{35}S (1000 Ci/mmol) sulphur in type I collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO_2.

[0109] The night before initiating the assay, chondrocyte monolayers are washed two times in DMEM/1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.

[0110] The following morning chondrocytes are washed once in DMEM/1%PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions.

[0111] Media and dilutions can be made as described in the Table below.

Control Media	DMEM alone (control media)
IL-1 Media	DMEM + IL-1 (5 ng/ml)
Drug Dilutions	Make all compounds stocks at 10 mM in DMSO. Make a 100 uM stock of each compound in DMEM in 96 well plate. Store in freezer overnight. The next day perform serial dilutions in DMEM with IL-1 to 5 uM, 500 nM, and 50 nM. Aspirate final wash from wells and add 50 ul of compound from above dilutions to 450 ul of IL-1 media in appropriate wells of the 48 well plates. Final compound concentrations equal 500 nM, 50 nM, and 5 nM. All samples completed in triplicate with Control and IL-1 alone samples on each plate.

[0112] Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns are periodically counted to monitor 35S-proteoglycan release. Control and IL-1 media are added to wells (450 ul) followed by compound (50 ul) so as to initiate the assay. Plates are incubated at 37°C, with a 5% CO_2 atmosphere.

[0113] At 40-50 % release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (9-12 hours). Media is removed from all wells and placed in scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 ul of papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT, and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added, and samples counted (LSC).

[0114] The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

[0115] For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the compounds of the invention (hereinafter also known as the active compounds) will be administered at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the ap-

propriate dose for the individual subject.

[0116] The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

[0117] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

[0118] For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

[0119] The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0120] For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

[0121] The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

Example 1

(2*R*,4*S*)-4-(4-Methoxyphenyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide

Step A: (5*R*)-3-Bromo-5-(tert-butyl-dimethylsilanyloxymethyl)-2-oxo-2,5-dihydropyrrole-1-carboxylic acid tert-butyl ester

[0122] A solution of 2-(tert-butyldimethylsilanyloxymethyl)-5-oxopyrrolidine-1-carboxylic acid tert-butyl ester (16.5 grams, 50 mmol) in tetrahydrofuran (800 mL) was cooled in bath at -78° C. A 1 M solution of lithium bis(trimethylsilyl) amide in tetrahydrofuran (100 mL, 100 mmol) was added slowly. After stirring for 2 hours, a solution of phenylselenyl-bromide (14.16 grams, 60 mmol) in tetrahydrofuran (100 mL) was added and, after 15 minutes, a solution of 1,2-dibromotetrachloroethane (19.5 grams, 60 mmol) in tetrahydrofuran (100 mL) was added. The reaction mixture was stirred for an additional 1.5 hours while cooling at -78° and was quenched by addition of saturated ammonium chloride solution. Water and diethyl ether were added. The aqueous phase was separated and extracted with diethyl ether. The combined organic layers were concentrated to an orange oil which was dissolved in methylene chloride (1000 mL). A

30% w/v aqueous solution of hydrogen peroxide (20 mL) was added and the mixture was stirred vigorously overnight. Water (50 mL) was added. The aqueous layer was separated and extracted with methylene chloride. The combined organic layers were dried over magnesium sulfate and concentrated to an orange oil. The title compound (12.0 grams, 59%) was isolated by flash chromatography on silica gel eluting first with a 1:1 mixture of hexane and methylene chloride and then with methylene chloride alone.

[0123] ^{1}H NMR ($CDCl_3$): δ 7.31 (d, J = 2.3 Hz, 1 H), 4.56 - 4.53 (m, 1 H), 4.08 (dd, J = 3.4, 10.0 Hz, 1 H), 3.74 (dd, J = 6.2, 10.0 Hz, 1 H), 1.53 (s, 9 H), 0.83 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

[0124] ^{13}C NMR ($CDCl_3$): δ 164.0, 149.1, 146.3, 118.2, 83.6, 62.8, 61.8, 28.0, 25.6, 18.0,-5.6, -5.7.

Step B: (5*R*)-5-(tert-Butyl-dimethylsilanyloxymethyl)-3-(4-methoxyphenyl)-2-oxo-2,5-dihydropyrrole-1-carboxylic acid tert-butyl ester

[0125] The diethanolamine complex of 4-methoxyphenyl boronic acid (2.5 grams, 11 mmol) was stirred in a mixture of diisopropyl ether (50 mL) and 1.5 M aqueous hydrochloric acid solution (30 mL) for 2 hours. After separation of the aqueous layer, toluene (50 mL) was added and the mixture was concentrated to remove most of the diisopropyl ether. (5*R*)-3-Bromo-5-(tert-butyl-dimethylsilanyloxymethyl)-2-oxo-2,5-dihydropyrrole-1-carboxylic acid tert-butyl ester (3.0 grams, 7.38 mmol), toluene (150 mL), and a solution of sodium carbonate (850 mg, 8 mmole) in water (20 mL) were added. After purging the solution of oxygen, tetrakis(triphenylphosphene)palladium (0) (250 mg) was added and the mixture was heated at reflux for 2.5 hours. The mixture was cooled and diluted with toluene and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated to a brown oil. The title compound (1.7 grams, 53%), was isolated by flash chromatography on silica gel eluting with methylene chloride.

[0126] ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J = 8.9 Hz, 2 H), 7.24 (d, J = 2.5 Hz, 1 H), 6.88 (d, J = 8.9 Hz, 2 H), 4.57 - 4.54 (m, 1 H), 4.17 (dd, J = 3.6, 9.6 Hz, 1 H), 3.79 (s, 3 H), 3.72 (dd, J = 6.6, 9.6 Hz, 1 H), 1.55 (s, 9 H), 0.82 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

Step C: (3S , 5*R*)-5-Hydroxymethyl-3-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylic acid tert-butyl ester

[0127] A solution of (5*R*)-5-(tert-butyl-dimethylsilanyloxymethyl)-3-(4-methoxyphenyl)-2-oxo-2,5-dihydropyrrole-1-carboxylic acid tert-butyl ester (1.7 grams, 3.9 mmol) in ethanol (100 mL) was treated with palladium black (300 mg) and hydrogenated in a Parr™ shaker at 3 atmospheres pressure overnight. The catalyst was removed by filtration and the solvent was evaporated to provide crude (3S, 5*R*)-5-(tert-butyl-dimethylsilanyloxymethyl)-3-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylic acid tert-butyl ester as an oil. This was dissolved in tetrahydrofuran (40 mL) and treated with aqueous 0.5 M hydrochloric acid solution (7.2 mL). The resulting mixture was stirred at room temperature overnight, quenched with saturated sodium carbonate solution and extracted twice with methylene chloride. The combined organic extracts were dried over magnesium sulfate and concentrated to an oil. The title compound (551 mg, 48%) was isolated by flash chromatography on silica gel eluting with 20% hexane in ethyl acetate.

[0128] ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J = 8.7 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 4.18 - 4.13 (m, 1 H), 3.81 - 3.65 (m, 4 H), 3.76 (s, 3 H, overlapped), 2.58 - 2.51 (m, 1 H), 1.96 - 1.87 (m, 1 H), 1.52 (s, 9H).

Step D: (2*R*, 4*S*)-4-(4-Methoxyphenyl)-5-oxopyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

[0129] A stock solution containing 12.0 grams of periodic acid and chromium trioxide (24 mg) in wet acetonitrile (0.75 volume % water) was prepared. A portion of this solution (9.6 mL) was added to a solution of (3S, 5*R*)-5-hydroxymethyl-3-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylic acid tert-butyl ester (510 mg, 1.58 mmol) in wet acetonitrile (0.75 volume % water) at 0° C. The reaction mixture was stirred at 0° C for 2 hours and then quenched by addition of a solution of dibasic sodium phosphate (1.2 grams) in water (20 mL). The mixture was extracted with ethyl acetate and the organic extract was washed with aqueous sodium bisulfite solution and brine. After drying over magnesium sulfate, the solvent was evaporated to provide the title compound as a white solid, 518 mg (98%).

[0130] ^{1}H NMR ($CDCl_3$): δ 8.56 (br s, 1 H), 7.13 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 4.58 (apparent t, J = 8.3 Hz, 1 H), 3.78 - 3.73 (m, 1 H), 3.73 (s, 3 H), 2.86 - 2.79 (m, 1 H), 2.13 - 2.05 (m, 1 H), 1.45 (s, 9 H).

[0131] ^{13}C NMR ($CDCl_3$): δ 176.2, 173.2, 159.0, 149.4, 129.2, 129.0, 114.2, 84.3, 56.8, 55.2, 47.9, 30.2, 27.8.

[0132] MS m/z 334 (M - 1), 234.

[0133] $[\alpha]_D$ = +4.4° (c = 1.12, $CHCl_3$).

Step E: (3*S*, 5*R*)-5-benzyloxycarbamoyl-3-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylic acid tert-butyl ester

[0134] To a solution of (2*R*, 4*S*)-4-(4-methoxyphenyl)-5-oxopyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (305

mg, 0.91 mmol), diisopropylethylamine (0.35 mL, 2.0 mmol) and O-benzylhydroxylamine hydrochloride (160 mg, 1.0 mmol) in methylene chloride (20 mL) was added (benztriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluoroborate (443 mg, 1.0 mmol). The reaction was stirred at room temperature overnight. After dilution with methylene chloride, the mixture was washed with aqueous saturated sodium bicarbonate solution, water and brine. The solution was dried over magnesium sulfate and concentrated to a white solid from which the title compound (294 mg, 73%) was isolated by flash chromatography eluting with 25% hexane in ethyl acetate.

[0135] MS m/z 439 (M - 1), 339.

Step F: (2*R*, 4*S*)-4-(4-Methoxyphenyl)-5-oxopyrrolidine-2-carboxylic acid benzyloxyamide

[0136] Hydrogen chloride gas was bubbled for 3 minutes through a solution of (3*S*, 5*R*)-5-benzyloxycarbamoyl-3-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylic acid tert-butyl ester (270 mg, 0.61 mmol) in methylene chloride (40 mL). After stirring for an additional 10 minutes, the solvent was evaporated to leave a white foam. The title compound (169 mg, 80%) was isolated by flash chromatography (eluting with ethyl acetate) and recrystallization from a mixture of ethyl acetate and hexane.

[0137] ^{1}H NMR ($CDCl_3$): δ 10.40 (br s, 1 H), 7.30 - 7.23 (m, 5 H), 7.15 (br s, 1 H), 7.04 (d, J = 8.5 Hz, 2 H), 6.76 (d, J = 8.5 Hz, 2 H), 4.79 - 4.72 (m, 2 H), 3.89 (apparent t, J = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.45 (apparent t, J = 9.6 Hz, 1 H), 2.77 - 2.69 (m, 1 H), 2.06 - 1.98 (m, 1 H).

[0138] ^{13}C NMR ($CDCl_3$): δ 179.1, 169.3, 158.8, 134.9, 130.0, 129.3, 129.2, 128.7, 128.5, 114.2, 78.1, 55.2, 53.9, 46.6, 34.6.

[0139] MS m/z 341 (M + 1).

[0140] $[\alpha]_D$ = +39.9° (c = 0.91, $CHCl_3$).

(2*R*, 4*S*)-4-(4-Methoxyphenyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide

[0141] A solution of (2*R*, 4*S*)-4-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylic acid benzyloxyamide (150 mg, 0.44 mmol) in methanol (15 mL) was treated with 5% palladium on barium sulfate (40 mg) and hydrogenated in a Parr™ shaker at 3 atmospheres pressure for 2.5 hours. The catalyst was removed by filtration and the solvent was evaporated to provide a solid. The title compound (106 mg, 96%) was isolated by crystallization from a mixture of ethyl acetate and hexane.

[0142] ^{1}H NMR (DMSO-d_6): δ 10.77 (br s, 1H), 8.97 (br s, 1 H), 8.01 (br s, 1 H), 7.14 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 8.4 Hz, 2 H), 3.91 (apparent t, J = 7.8 Hz, 1 H), 3.69 (s, 3 H), 3.53 (apparent t, J = 7.8 Hz, 1 H), 2.67 - 2.58 (m, 1 H), 1.92 - 1.84 (m, 1 H).

[0143] MS m/z 249 (M - 1).

Example 2

(2*R*, 4*S*)-4-[4-(4-Fluorophenoxy)phenyl]-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide

[0144] Prepared according to the method of Example 1 starting with the diethanolamine complex of 4-(4-fluorophenoxy)phenyl boronic acid.

[0145] ^{1}H NMR (DMSO-d_6): δ 10.78 (br s, 1 H), 8.98 (br s, 1 H), 8.06 (s, 1 H), 7.23 (d, J = 8.7 Hz, 2H), 7.19 - 7.15 (m, 2 H), 7.02 - 6.98 (m, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 3.91 (apparent t, J = 7.8 Hz, 1 H), 3.59 (apparent t, J = 9.8 Hz, 1 H), 2.67 - 2.60 (m, 1 H), 1.94 - 1.86 (m, 1H).

[0146] ^{13}C NMR (DMSO-d_6): δ 176.0, 167.8, 157.6 (d, J = 240 Hz), 155.2, 152.3, 134.8, 129.4, 119.9 (d, J = 9 Hz), 117.5, 116.0 (d, J = 23 Hz), 51.4, 45.5, 33.6.

[0147] MS m/z 329 (M - 1).

[0148] $[\alpha]_D$ = +24.3° (c = 1.14, MeOH).

Example 3

(2*R*, 4*S*)-4-(4'-Fluorobiphenyl-4-yl)-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide

[0149] Prepared according to the method of Example 1 starting with the diethanolamine complex of 4'-fluorobiphen-4-yl boronic acid. Recrystallized from methanol, mp: 193-202° C.

[0150] ^{1}H NMR (DMSO-d_6): δ 10.77 (br s, 1H), 8.97 (br s, 1 H), 8.08 (s, 1 H), 7.67 - 7.63 (m, 2 H), 7.55 (d, J = 8.1 Hz, 2 H), 7.32 (d, J = 8.1 Hz, 2 H), 7.24 (apparent t, J = 8.8 Hz, 2 H), 3.95 (apparent t, J = 7.8 Hz, 1 H), 3.65 (apparent t, J = 9.7 Hz, 1 H), 2.71 - 2.64 (m, 1 H), 2.00 - 1.93 (m, 1 H).

[0151] MS: m/z 313 (M - 1).

[0152] Analysis calculated for $C_{17}H_{15}FN_2O_3$. ½ H20: C, 63.15; H, 4.99; N, 8.66. Found: C, 62.83; H, 5.48; N, 8.39.

Example 4

(2*R*, 4*S*)-4-[3-(4-Fluorophenoxy)phenyl]-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide

[0153] Prepared according to the method of Example 1 starting with the diethanolamine complex of 3-(4-fluorophenoxy)phenyl boronic acid. Recrystallized from ethyl acetate, mp: 151-152° C.

[0154] ^{1}H NMR (DMSO-d_6): δ 10.79 (s, 1 H), 8.98 (s, 1 H), 8.08 (s, 1 H), 7.28 (apparent t, J = 7.9 Hz, 1 H), 7.22 - 7.18 (m, 2 H), 7.04 - 7.01 (m, 3 H), 6.93 (apparent s, 1 H), 6.78 (dd, J = 2.5, 8.3 Hz, 1 H), 3.91 (apparent t, J = 7.6 Hz, 1 H), 3.62 (apparent t, J = 9.8 Hz, 1 H), 2.69 - 2.62 (m, 1 H), 1.95 - 1.87 (m, 1 H).

[0155] MS: m/z 329 (M - 1).

[0156] $[\alpha]_D$ = +17.9° (c = 1.00, MeOH)

[0157] Analysis calculated for $C_{17}H_{15}FN_2O_4$: C, 61.82; H, 4.58; N, 8.48. Found: C, 61.85; H, 4.59; N, 8.40.

Example 5

(2*R*, 4*S*)-4-Naphthalen-2-yl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide

[0158] Prepared according to the method of Example 1 starting with 2-naphthyl boronic acid. Recrystallized from ethyl acetate/methanol, mp: 197-199° C.

[0159] ^{1}H NMR (DMSO-d_6): δ 10.82 (br s, 1 H), 9.00 (s, 1 H), 8.14 (s, 1 H), 7.86 - 7.83 (m, 3 H), 7.75 (apparent s, 1 H), 7.46 - 7.42 (m, 3 H), 4.00 (apparent t, J = 7.6 Hz, 1 H), 3.80 (apparent t, J = 9.6 Hz, 1 H), 2.77 - 2.72 (m, 1 H), 2.10 - 2.03 (m, 1 H).

[0160] MS: m/z 269 (M - 1).

[0161] $[\alpha]_D$ = 0° (c = 0.33, MeOH)

[0162] Analysis calculated for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.43; H, 5.41; N, 10.10.

Example 6

(2*R*, 4*S*)-5-Oxo-4-(4-phenethylphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide

[0163] Prepared according to the method of Example 1 starting with 4-styrylphenyl boronic acid. (The styryl double bond is reduced to a phenethylphenyl group at the same time the 2-oxo-2,5-dihydropyrrole double bond is hydrogenated.)

[0164] ^{1}H NMR (DMSO-d_6): δ 10.78 (br s, 1 H), 8.97 (s, 1 H), 8.03 (s, 1 H), 7.24 - 7.22 (m, 4 H), 7.14 (apparent s, 5 H), 3.92 (apparent t, J = 7.4 Hz, 1 H), 3.55 (apparent t, J = 9.9 Hz, 1 H), 2.82 (apparent s, 4 H), 2.67 - 2.60 (m, 1 H), 1.95 - 1.87 (m, 1 H).

[0165] MS: m/z = 325 (M + 1).

Example 7

(2*R*, 4*S*)-4-(4-Benzyloxyphenyl)-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide

Step A: (5*R*)-3-(4-Benzyloxyphenyl)-5-(tert-butyldimethylsilanyloxymethyl)-2-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester

[0166] The diethanolamine complex of 4-phenethylphenyl boronic acid (8.25 g, 27.8 mmol) was stirred in a mixture of diethyl ether (165 mL) and 3 M aqueous HCl solution (66 mL) for 3 hours. After separation of the aqueous layer, toluene (100 mL) was added and the mixture was concentrated to remove most of the diethyl ether. (5R)-3-Bromo-5-(tert-butyldimethylsilanyloxymethyl)-2-oxo-2,5-dihydropyrrole-1-carboxylic acid tert-butyl ester (7.5 g, 18.5 mmol) and a solution of Na_2CO_3 (1.25 g, 11.8 mmole) in water (25 mL) were added. After purging the solution of oxygen, tetrakis (triphenylphosphene)palladium (0) (424 mg) was added and the mixture was heated at reflux for 18 h. The mixture was cooled and diluted with toluene and water. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to a dark oil. The title compound (5.5 g, 58%), was isolated as a pale yellow solid by flash chromatography on silica gel eluting 15% diethyl ether in hexane.

Step B: (3*S*,5*R*)-3-(4-Benzyloxyphenyl)-5-(tert-butyldimethylsilanyloxymethyl)-2-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester

[0167] A solution of (5*R*)-3-(4-benzyloxyphenyl)-5-(tert-butyldimethylsilanyloxymethyl)-2-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (2.0 g, 3.92 mmol) in ethyl acetate (40 mL) and hexane (40 mL) was treated with 20% palladium hydroxide on carbon (200 mg) and hydrogenated in a Parr™ shaker at 3 atmospheres pressure for 2 hours. The catalyst was removed by filtration and the solvent was evaporated to provide the title compound as a yellow oil (2.0 g, 100%).

Step C: (3*S*,5*R*)-3-(4-Benzyloxyphenyl)-5-hydroxymethyl-2-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester

[0168] A solution of (3*S*,5*R*)-3-(4-benzyloxyphenyl)-5-(tert-butyldimethylsilanyloxymethyl)-2-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (2.0 g, 3.91 mmol) in tetrahydrofuran (45 mL) was cooled in an ice bath. Aqueous 0.5 M HCl solution (7.8 mL, 3.9 mmol) was added and the resulting mixture was allowed to warm to room temperature while stirring overnight. After a total reaction time of 24 hours, saturated aqueous $NaHCO_3$ solution was added. The mixture was extracted twice with diethyl ether and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated to an oil. The title compound, a colorless oil (1.02 g, 65%), was isolated by flash chromatography on silica gel eluting with 50% ethyl acetate in hexane.

Step D: (2*R*, 4*S*)-4-(4-Benzyloxyphenyl)-5-oxo-pyrrolidine-2-carboxylic acid

[0169] A solution containing 6.0 g of periodic acid and chromium trioxide (13 mg) in wet acetonitrile (60 mL; 0.75 volume % water) was prepared. A portion of this solution (15 mL) was added dropwise to a solution of (3*S*,5*R*)-3-(4-benzyloxyphenyl)-5-hydroxymethyl-2-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (1.02 g, 2.57 mmol) in wet acetonitrile (15 mL; 0.75 volume % water) at 0° C. The reaction mixture was stirred at 0° C for 2 hours. At this time, more of the periodic acid/chromium trioxide solution (5 mL) was added. Stirring at 0° C was continued for an additional 1 hour. After quenching with a solution of dibasic sodium phosphate (720 mg) in water (12 mL), the mixture was extracted twice with diethyl ether. The combined organic extracts were washed with aqueous sodium bisulfite solution (440 mg in 10 mL water) and brine. After drying over $MgSO_4$, the solvent was evaporated to provide a yellow solid that was taken up in methylene chloride (100 mL) and cooled in an ice bath. Hydrogen chloride gas was bubbled through the cold solution for 2 minutes and the resulting mixture was stirred at 0° C for 1 hour. The solvent and HCl were evaporated to afford a solid from which the title compound, 226 mg (28%) was isolated by trituration with a mixture of methylene chloride, diethyl ether and ethyl acetate. The trituration filtrate was dissolved in aqueous saturated $NaHCO_3$ solution and washed twice with diethyl ether. After careful acidification with aqueous 6 M HCl solution, the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to provide more of the title compound, 123 mg (15%).

Step E: (2*R*, 4*S*)-4-(4-Benzyloxyphenyl)-5-oxo-pyrrolidine-2-carboxylic acid (2-trimethylsilanylethoxy)amide

[0170] To a solution of (2*R*, 4*S*)-4-(4-benzyloxyphenyl)-5-oxo-pyrrolidine-2-carboxylic acid (330 mg, 1.06 mmol), N-methyl morpholine (0.25 mL, 2.3 mmol) and O-(2-trimethylsilylethyl) hydroxylamine hydrochloride (220 mg, 1.30 mmol) in CH_2Cl_2 (20 mL) was added (benztriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluoroborate (560 mg, 1.27 mmol). The reaction was stirred at room temperature for 6 hours. After dilution with CH_2Cl_2, the mixture was washed sequentially with aqueous 0.5 M HCl solution, water, aqueous saturated $NaHCO_3$ solution, and brine. The solution was dried over $MgSO_4$ and concentrated to a white solid that was triturated with ethyl acetate and set aside. The trituration filtrate was concentrated and chromatographed on silica gel eluting with 5% methanol in chloroform. Fractions containing the title compound were combined and concentrated to afford a white solid that was combined with the solid obtained directly from the crude product mixture. The sample was stirred in water overnight. The title compound was collected by filtration and dried. The yield was 194 mg (43%).

Step F: (2*R*, 4*S*)-4-(4-Benzyloxyphenyl)-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide

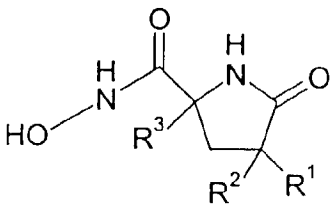
[0171] To a suspension of (2*R*, 4*S*)-4-(4-benzyloxyphenyl)-5-oxo-pyrrolidine-2-carboxylic acid (2-trimethylsilanylethoxy)amide (95 mg, 0.22 mmol) in methylene chloride was added boron trifluoride etherate (0.86 µL, 0.68 mmol). The mixture was stirred at room temperature for 75 minutes. During this period the suspended solid dissolved completely and the product precipitated. The mixture was quenched by addition of saturated aqueous NH_4Cl solution. The title compound was collected by filtration, washing well with ethyl acetate and water, and dried. The yield was 56 mg (78%).

[0172] ^{1}H NMR (DMSO-d_6): δ 10.74 (br s, 1 H), 8.95 (br s, 1 H), 8.00 (br s, 1 H), 7.70 - 7.27 (m, 5 H), 7.13 (d, J = 8.0 Hz, 2 H), 6.91 (d, J = 8.0 Hz, 2 H), 5.04 (apparent s, 2 H), 3.89 (apparent t, J = 7.7 Hz, 1 H), 3.51 (apparent t, J = 9.7 Hz, 1 H), 2.64 - 2.57 (m, 1 H), 1.91 - 1.83 (m, 1 H).

[0173] MS: m/z 325 (M - 1).

Claims

1. A compound of the formula



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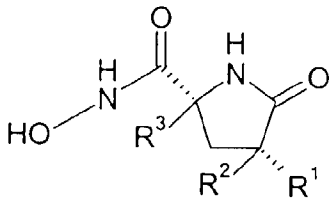
wherein R^1 is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_1-C_6)alkyl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl or (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, wherein each of said (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy; and

R^2 and R^3 are independently selected from H, (C_1-C_6)alkyl, and CH_2(C_6-C_{10})aryl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, wherein each (C_6-C_{10})aryl or (C_2-C_9)heteroaryl moieties of said (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryloxy(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl, (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, or (C_2-C_9)heteroaryl(C_1-C_6)alkoxy(C_2-C_9)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring independently selected from fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_3)alkyl, perfluoro(C_1-C_3)alkoxy and (C_6-C_{10})aryloxy.

3. A compound according to claim 1 with the stereochemistry



I'

4. A compound according to claim 3, wherein R^1 is optionally substituted $(C_6\text{-}C_{10})$aryl.

5. A compound according to claim 3, wherein R^1 is optionally substituted $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl.

6. A compound according to claim 3, wherein R^1 is optionally substituted $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl.

7. A compound according to claim 3, wherein R^1 is optionally substituted $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl.

8. A compound according to claim 3, wherein said R^1 optional substituent is hydrogen, fluoro, chloro, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy.

9. A compound according to claim 3, wherein said R^1 optional substituent is in the para position of the terminal ring.

10. A compound according to claim 3, wherein said R^1 optional substituent is in the ortho position of the terminal ring.

11. A compound according to claim 3 wherein R^2 and R^3 are hydrogen.

12. A compound according to claim 3 wherein one or both of R^2 and R^3 are independently selected from $(C_1\text{-}C_6)$alkyl, and $CH_2(C_6\text{-}C_{10})$aryl.

13. A compound according to claim 3, wherein said compound is selected from the group consisting of:

(2*R*, 4*S*)-4-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-fluorophenoxy)phenyl]-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-5-oxo-4-(4-phenoxyphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-chlorophenoxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[3-(4-chlorophenoxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[3-(4-fluorophenoxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-5-oxo-4-[4-(pyridin-4-yloxy)-phenyl]pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-biphenyl-4-yl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4'-fluorobiphenyl-4-yl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4-benzyloxyphenyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-5-oxo-4-(4-phenethylphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-fluorobenzyloxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(3,5-difluorobenzyloxy)phenyl]-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4-methoxybenzyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-(4'-fluorobiphenyl-4-ylmethyl)-5-oxopyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-naphthalen-2-yl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide;
(2*R*, 4*S*)-4-[4-(4-fluorophenoxy)-phenyl]-2,4-dimethyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-fluorophenoxy)-phenyl]-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*R*)-4-benzyl-5-oxo-4-(4-phenoxyphenyl)-pyrrolidine-2-carboxylic acid hydroxyamide,
(2*R*, 4*S*)-4-[4-(4-chlorophenoxy)phenyl]-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide, and
(2*R*, 4*S*)-4-[4-(4-chlorophenoxy)phenyl]-2,4-dimethyl-5-oxo-pyrrolidine-2-carboxylic acid hydroxyamide.

14. A pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic an-

eurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

15. A method for treating a condition selected from the group consisting of arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis and septic shock in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

16. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of matrix metalloproteinases in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of a mammalian reprolysin in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

18. A method for the inhibition of matrix metalloproteinases in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

19. A method for the inhibition of a mammalian reprolysin in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

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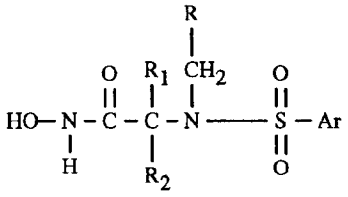
(54) **Arylsulfonamido-substituted hydroxamic acids.**

(57) Compounds of formula I



(I)

wherein R, R_1, R_2 and Ar are as defined in the description, have valuable pharmaceutical properties and are effective especially as matrix metalloproteinase inhibitors, for example for the treatment of arthritis. They are prepared in a manner known per se.

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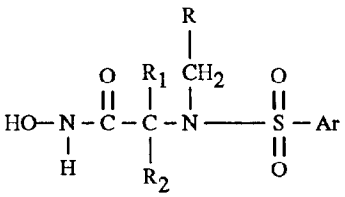
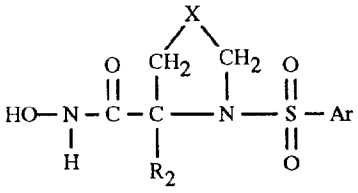
The present invention relates to the compounds of formula I



(I)

(a) wherein
Ar is carbocyclic or heterocyclic aryl;
R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;
R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, (carbocyclic or heterocyclic aryl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl or N-lower alkylpiperidyl;
R_2 is hydrogen or lower alkyl;
(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);
(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);
pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof;
further to a process for the preparation of these compounds, to pharmaceutical compositions comprising these compounds, to the use of these compounds for the therapeutic treatment of the human or animal body or for the manufacture of a pharmaceutical composition.

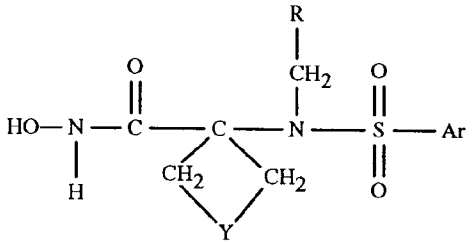
The compounds of formula I defined under (b) above can be represented by formula Ia



(Ia)

wherein X represents methylene or 1,2-ethylene each unsubstituted or substituted by lower alkyl, or X represents oxygen, sulfur, or 1,2-phenylene; and Ar and R_2 have meaning as defined above.

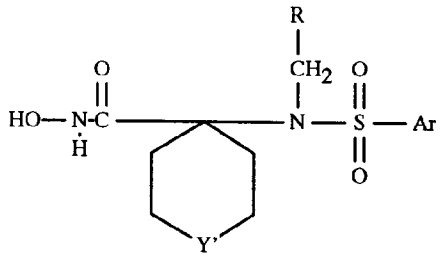
The compounds of formula I defined under (c) above can be represented by formula Ib



(Ib)

wherein Y is a direct bond, C_1-C_4-straight chain alkylene optionally substituted by lower alkyl, CH_2OCH_2, CH_2SCH_2, 1,2-phenylene, CH_2-1,2-phenylene or $CH_2N(R_6)$-CH_2 in which R_6 represents hydrogen, lower alkanoyl, di-lower alkylamino-lower alkanoyl, aroyl, carbocyclic aryl-lower alkanoyl, lower alkyl, carbocyclic or heterocylic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or lower alkylsulfonyl; and Ar and R have meaning as defined above.

A preferred embodiment of the compounds of formula Ib relates to the compounds of formula Ic



(Ic)

in which Y' represents oxygen, sulfur, a direct bond, methylene or methylene substituted by lower alkyl, or NR_6; R_6 represents hydrogen, lower alkanoyl, di-lower alkylamino-lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or lower alkylsulfonyl; Ar and R have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof.

Preferred are said compounds of formula I, Ia, Ib and Ic wherein Ar is monocyclic carbocyclic aryl such as phenyl or phenyl mono-, di- or tri-substituted by C_1-C_{10}-alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, C_3-C_7-cycloalkyl-lower alkoxy, (lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl or C_3-C_7-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino or mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is heterocyclic monocyclic aryl such as thienyl or thienyl substituted by lower alkyl; the other symbols have meaning as defined; pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_{10}-alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen;

C_3-C_7-cycloalkyl-lower alkoxy, (lower alkyl, phenyl-lower alkyl or C_3-C_7-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenylyl

which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluormethyl or cyano; biphenylyl-lower alkyl wherein biphenylyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluormethyl or cyano; (pyridyl, thienyl, quinolinyl or thiazolyl)-lower alkyl, trifluormethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; pyridyl, thienyl, biphenylyl, biphenylyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; trifluoromethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, lower alkanoylamino-lower alkyl; R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl or N-lower alkylpiperidyl;

R_2 is hydrogen or lower alkyl;

(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, benzyloxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Especially preferred are the compounds of formula I wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_7-alkoxy, hydroxy, phenyl-lower alkoxy, C_3-C_7-cycloalkyl-lower alkoxy, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl; biphenylyl; biphenylyl-lower alkyl; (pyridyl or thienyl)-lower alkyl, trifluormethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_5-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy; biphenylyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, lower alkanoylamino-lower alkyl; R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl or N-lower alkylpiperidyl;

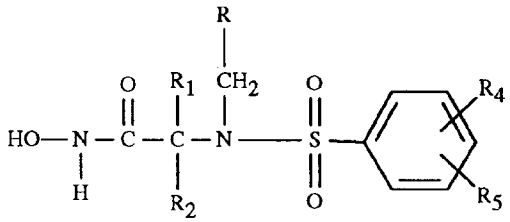
R_2 is hydrogen or lower alkyl;

(b) or wherein R and R_1 together with the chain to which they are attached form a thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

A particular embodiment of the invention relates to the compounds of formula II



(II)

wherein

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_5-C_7-cycloalkyl, C_5-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, piperidyl, N-lower alkylpiperidyl, or acylamino-lower alkyl represented by R_3-CONH-lower alkyl;

R_2 is hydrogen;

R_3 in R_3-CONH-lower alkyl is lower alkyl, carbocyclic or heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkyl-piperidyl)-lower alkyl;

R_4 is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;

R_5 is hydrogen, lower alkyl or halogen;

or R_4 and R_5 together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;

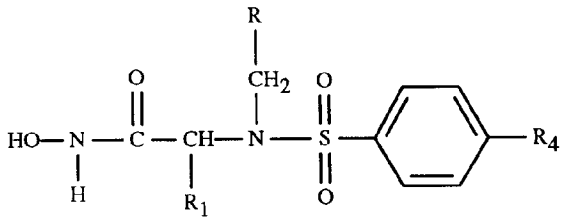
or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the invention relates to the compounds of formula II wherein R and R_1 together with the chain to which they are attached form an 1,2,3,4-tetrahydro-isoquinoline, piperidine, thiazolidine or pyrrolidine ring; and R_2, R_4 and R_5 have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof. Such compounds correspond to compounds of formula Ia wherein Ar is optionally substituted phenyl as defined above.

Another preferred embodiment of the invention relates to the compounds of formula II wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from cyclohexane, cyclopentane, oxacyclohexane, thiacyclohexane, indane, tetralin, piperidine or piperidine substituted on

nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl or by lower alkylsulfonyl; and R, R_4 and R_5 have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof. Such compounds correspond to compounds of formula Ib wherein Ar is optionally substituted phenyl as defined above.

Particularly preferred are the compounds of formula III



(III)

wherein R represents lower alkyl, trifluoromethyl, C_5-C_7-cycloalkyl, (oxa or thia)-C_4-C_5-cycloalkyl, biaryl, carbocyclic monocyclic aryl or heterocyclic monocyclic aryl; R_1 represents hydrogen, lower alkyl, C_5-C_7-cycloalkyl, monocyclic carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, di-lower alkylamino-lower alkyl, (N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino)-lower alkyl or R_3-CONH-lower alkyl; R_3 represents lower alkyl, carbocyclic aryl, heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; R_4 represents lower alkoxy or carbocyclic or heterocyclic aryl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Further preferred are compounds of formula III wherein R represents monocyclic carbocyclic aryl or monocyclic heterocyclic aryl; R_1 and R_4 have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof.

More particularly preferred are said compounds of formula III wherein R represents heterocyclic monocyclic aryl selected from tetrazolyl, triazolyl, thiazolyl, imidazolyl and pyridyl, each unsubstituted or substituted by lower alkyl; or R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R_1 represents lower alkyl, cyclohexyl, or R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; and R_4 represents lower alkoxy or phenyl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

A further preferred embodiment relates to said compounds of formula III wherein R represents 2-, 3- or 4-pyridyl or phenyl; R_1 represents C_1-C_4-alkyl, cyclohexyl or R_3-CONH-C_1-C_4-alkyl wherein R_3 represents di-C_1-C_4-alkylamino-C_1-C_4-lower alkyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Particularly preferred are said compounds of formula III wherein R represents 3-pyridyl or 4-pyridyl; R_1 represents isopropyl or cyclohexyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

The invention relates especially to the specific compounds described in the examples, pharmaceutically acceptable prodrug derivatives thereof and pharmaceutically acceptable salts thereof, and in particular to the specific compounds described in the examples and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable prodrug derivatives are those that may be convertible by solvolysis or under physiological conditions to the free hydroxamic acids of the invention and represent such hydroxamic acids in which the CONHOH group is derivatized in form of an O-acyl or an optionally substituted O-benzyl derivative. Preferred are the optionally substituted O-benzyl derivatives.

The compounds of the invention depending on the nature of the substituents, possess one or more asymmetric carbon atoms. The resulting diastereoisomers and enantiomers are encompassed by the instant invention.

Preferred are the compounds of the invention wherein the asymmetric carbon in the above formulae (to which are attached R_1 and/or R_2) corresponds to that of a D-aminoacid precursor and is assigned the (R)-configuration.

The general definitions used herein have the following meaning within the scope of the present invention, unless otherwise specified.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms, and represents for example methyl, ethyl, propyl, butyl, isopropyl or isobutyl.

A lower alkoxy (or alkyloxy) group preferably contains 1-4 carbon atoms, advantageously 1-3 carbon atoms, and represents for example ethoxy, propoxy, isopropoxy, or most advantageously methoxy.

Halogen (halo) preferably represents chloro or fluoro but may also be bromo or iodo.

Mono- or poly-halo-lower alkyl represents lower alkyl preferably substituted by one, two or three halogens, preferably fluoro or chloro, e.g. trifluoromethyl or trifluoroethyl.

Aryl represents carbocyclic or heterocyclic aryl.

Prodrug acyl derivatives are preferably those derived from an organic carbonic acid, an organic carboxylic acid or a carbamic acid.

An acyl derivative which is derived from an organic carboxylic acid is, for example, lower alkanoyl, phenyl-lower alkanoyl or unsubstituted or substituted aroyl, such as benzoyl.

An acyl derivative which is derived from an organic carbonic acid is, for example, alkoxycarbonyl, especially lower alkoxycarbonyl, which is unsubstituted or substituted by carbocyclic or heterocyclic aryl or is cycloalkoxycarbonyl, especially C_3-C_7-cycloalkyloxycarbonyl, which is unsubstituted or substituted by lower alkyl.

An acyl derivative which is derived from a carbamic acid is, for example, amino-carbonyl which is substituted by lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, carbocyclic or heterocyclic aryl, lower alkylene or lower alkylene interrupted by O or S.

Prodrug optionally substituted O-benzyl derivatives are preferably benzyl or benzyl mono-, di-, or tri-substituted by e.g. lower alkyl, lower alkoxy, amino, nitro, halogen and/or trifluoromethyl.

Carbocyclic aryl represents monocyclic or bicyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from lower alkyl, lower alkoxy, hydroxy, halogen, cyano, trifluoromethyl, lower alkylenedioxy and oxy-C_2-C_3-alkylene; or 1- or 2-naphthyl. Lower alkylenedioxy is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy-C_2-C_3-alkylene is also a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. oxyethylene or oxypropylene. An example for oxy-C_2-C_3-alkylene-phenyl is 2,3-dihydrobenzofuran-5-yl.

Preferred as carbocyclic aryl is phenyl or phenyl monosubstituted by lower alkoxy, halogen, lower alkyl or trifluoromethyl, especially phenyl or phenyl monosubstituted by lower alkoxy, halogen or trifluoromethyl, and in particular phenyl.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxasolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by e.g. lower alkyl or halogen. Pyridyl represents 2-, 3- or 4-pyridyl, advantageously 2- or 3-pyridyl. Thienyl represents 2- or 3-thienyl, advantageously 2-thienyl. Quinolinyl represents preferably 2-, 3- or 4-quinolinyl, advantageously 2-quinolinyl. Isoquinolinyl represents preferably 1-, 3- or 4-isoquinolinyl. Benzopyranyl, benzothiopyranyl represent preferably 3-benzopyranyl or 3-benzothiopyranyl, respectively. Thiazolyl represents preferably 2- or 4-thiazolyl, advantageously 4-thiazolyl. Triazolyl is preferably 1-, 2- or 5-(1,2,4-triazolyl). Tetrazolyl is preferably 5-tetrazolyl. Imidazolyl is preferably 4-imidazolyl.

Preferably, heterocyclic aryl is pyridyl, quinolinyl, pyrrolyl, thiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by lower alkyl or halogen; and in particular pyridyl.

Biaryl is preferably carbocyclic biaryl, e.g. biphenyl, namely 2, 3 or 4-biphenyl, advantageously 4-biphenyl, each optionally substituted by e.g. lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano.

C_3-C_7-Cycloalkyl represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 to 7 ring carbons and is advantageously cyclopentyl or cyclohexyl optionally substituted by lower alkyl.

(Oxa or thia)-C_3-C_6-cycloalkyl represents a saturated cyclic radical wherein 1 or 2, preferably 1, oxygen or sulfur atom(s) and 3-6, preferably 4-5, carbon atoms form a ring, e.g. tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl or tetrahydrothienyl.

Oxa-cyclohexane means tetahydropyran, and thia-cyclohexane means tetrahydrothiopyran.

Carbocyclic aryl-lower alkyl represents preferably straight chain or branched aryl-C_1-C_4-alkyl in which carbocyclic aryl has meaning as defined above, e.g. benzyl or phenyl-(ethyl, propyl or butyl), each unsubstituted or substituted on phenyl ring as defined under carbocyclic aryl above, advantageously

optionally substituted benzyl.

Heterocyclic aryl-lower alkyl represents preferably straight chain or branched heterocyclic aryl-C_1-C_4-alkyl in which heterocyclic aryl has meaning as defined above, e.g. 2-, 3- or 4-pyridylmethyl or (2-, 3- or 4-pyridyl)-(ethyl, propyl or butyl); or 2- or 3-thienylmethyl or (2- or 3-thienyl)-(ethyl, propyl or butyl); 2-, 3- or 4-quinolinylmethyl or (2-, 3- or 4-quinolinyl)-(ethyl, propyl or butyl); or 2- or 4-thiazolylmethyl or (2- or 4-thiazolyl)-(ethyl, propyl or butyl).

Cycloalkyl-lower alkyl represents e.g. (cyclopentyl- or cyclohexyl)-(methyl or ethyl).

Biaryl-lower alkyl represents e.g. 4-biphenylyl-(methyl or ethyl).

Acyl is derived from an organic carboxylic acid, carbonic acid or carbamic acid.

Acyl represents e.g. lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkoxycarbonyl, aroyl, di-lower alkylaminocarbonyl or di-lower alkylamino-lower alkanoyl. Preferably, acyl is lower alkanoyl.

Acylamino represents e.g. lower alkanoylamino or lower alkoxycarbonylamino.

Acylamino-lower alkyl in R and R_1 is R_3-CONH-lower alkyl in which R_3 represents e.g. lower alkyl, lower alkoxy, aryl-lower alkyl, aryl-lower alkoxy, carbocyclic or heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkylpiperidyl)-lower alkyl.

Lower alkanoyl represents e.g. C_1-C_7-alkanoyl including formyl, and is preferably C_2-C_4-alkanoyl such as acetyl or propionyl.

Aroyl represents e.g. benzoyl or benzoyl mono- or di-substituted by one or two radicals selected from lower alkyl, lower alkoxy, halogen, cyano and trifluoromethyl; or 1- or 2-naphthoyl; and also e.g. pyridylcarbonyl.

Lower alkoxycarbonyl represents preferably C_1-C_4-alkoxycarbonyl, e.g. ethoxycarbonyl.

Lower alkylene represents either straight chain or branched alkylene of 1 to 7 carbon atoms and represents preferably straight chain alkylene of 1 to 4 carbon atoms, e.g. a methylene, ethylene, propylene or butylene chain, or said methylene, ethylene, propylene or butylene chain mono-substituted by C_1-C_3-alkyl (advantageously methyl) or disubstituted on the same or different carbon atoms by C_1-C_3-alkyl (advantageously methyl), the total number of carbon atoms being up to and including 7.

Esterified carboxyl is for example lower alkoxycarbonyl or benzyloxycarbonyl.

Amidated carboxyl is for example aminocarbonyl, mono- or di-lower alkylaminocarbonyl.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The compounds of the invention exhibit valuable pharmacological properties in mammals including man and are particularly useful as inhibitors of matrix-degrading metalloproteinase enzymes (= metalloproteinases).

Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (as reported in J. Leuk. Biol. 52 (2): 244-248, 1992).

As the compounds of the invention are inhibitors of stromelysin, gelatinase and/or collagenase activity and inhibit matrix degradation, they are particularly useful in mammals as agents for the treatment of e.g. osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, tumor metastasis, progression of HIV-infection and HIV-infection related disorders.

Illustrative of the matrix degrading metalloproteinase inhibitory activity, compounds of the invention prevent the degradation of cartilage caused by exogenous or endogenous stromelysin in mammals. They inhibit e.g. the stromelysin-induced degradation of aggrecan (large aggregating proteoglycan), link protein or type 1X collagen in mammals.

Beneficial effects are evaluated in pharmacological tests generally known in the art, and as illustrated herein.

The above-cited properties are demonstrable in in vitro and in vivo tests, using advantageously mammals, e.g. rats, guinea pigs, dogs, rabbits, or isolated organs and tissues, as well as mammalian

enzyme preparations. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally or parenterally, advantageously orally, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-5} molar and 10^{-10} molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 0.1 and 50 mg/kg.

One test to determine the inhibition of stromelysin activity is based on its hydrolysis of Substance P using a modified procedure of Harrison et al (Harrison, R.A., Teahan J., and Stein R., A semicontinuous, high performance chromatography based assay for stromelysin, Anal. Biochem. 180, 110-113 (1989)). In this assay, Substance P is hydrolyzed by recombinant human stromelysin to generate a fragment, Substance P 7-11, which can be quantitated by HPLC. In a typical assay, a 10 mM stock solution of a compound to be tested is diluted in the assay buffer to 50 μM, mixed 1:1 with 8 μg recombinant human stromelysin (mol. wt. 45-47 kDa, 2 Units; where 1 Unit produces 20 mmoles of Substance P 7-11 in 30 minutes) and incubated along with 0.5mM Substance P in a final volume of 0.125 ml for 30 minutes at 37 °C. The reaction is stopped by adding 10 mM EDTA and Substance P 7-11 is quantified on RP-8 HPLC. The IC_{50} for inhibition of stromelysin activity and Ki are calculated from control reaction without the inhibitor. Typically, Ki values of from 10 to 200 nM are obtained.

Stromelysin activity can also be determined using human aggrecan as a substrate. This assay allows the confirmation in-vitro that a compound can inhibit the action of stromelysin on its highly negatively-charged natural substrate, aggrecan (large aggregating prtoeoglycan). Within the cartilage, proteoglycan exists as an aggregate bound to hyaluronate. Human proteoglycan aggregated to hyaluronate is used as an enzyme substrate. The assay is set up in 96-well microtiter plates allowing rapid evaluation of compounds. The assay has three major steps:

1) Plates are coated with hyaluronate (human umbilical chord, 400 ug/ml), blocked with BSA (5 mg/ml), and then proteoglycan (human articular cartilage D1 - chondroitinase ABC digested, 2 mg/ml) is bound to the hyaluronate. Plates are washed between each step.

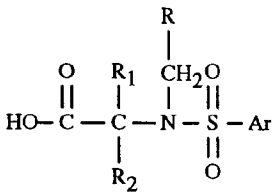
2) Buffers + inhibitor (1 to 5,000 nM) + recombinant human stromelysin (1-3 Units/well) are added to wells. The plates are sealed with tape and incubated overnight at 37 °C. The plates are then washed.

3) A primary (3B3) antibody (mouse IgM, 1:10,000) is used to detect remaining fragments. A secondary antibody, peroxididase-linked anti-IgM, is bound to the primary antibody. OPD is then added as a substrate for the peroxidase and the reaction is stopped with sulfuric acid. The IC_{50} for inhibition of stromelysin activity is graphically derived and Ki is calculated.

Collagenase activity is determined as follows: ninety six-well, flat-bottom microtiter plates are first coated with bovine type I collagen (35 ug/well) over a two-day period at 30 °C using a humidified and then dry atmosphere; plates are rinsed, air dried for 3-4 hours, sealed with Saran wrap and stored in a refrigerator. Human recombinant fibroblast collagenase and a test compound (or buffer) are added to wells (total volume = 0.1 ml) and plates are incubated for 2 hours at 35 °C under humidified conditions; the amount of collagenase used per well is that causing approximately 80% of maximal digestion of collagen. The incubation media are removed from the wells, which are then rinsed with buffer, followed by water. Coomasie blue stain is added to the wells for 25 minutes, removed, and wells are again rinsed with water. Sodium dodecyl sulfate (20% in 50% dimethylformamide in water) is added to solubilize the remaining stained collagen and the optical density at 570 nM wave length is measured. The decrease in optical density due to collagenase (from that of collagen without enzyme) is compared to the decrease in optical density due to the enzyme in the presence of test compound, and percent inhibition of enzyme activity is calculated. IC_{50}'s are determined from a range of concentrations of inhibitors (4-5 concentrations, each tested in triplicate), and K_i values are calculated.

The effect of compounds of the invention in-vivo can be determined in rabbits. Typically, four rabbits are dosed orally with a compound up to four hours before being injected intra-articularly in both knees (N = 8) with 40 Units of recombinant human stromelysin dissolved in 20 mM Tris, 10 mM $CaCl_2$, and 0.15 M NaCl at pH 7.5. Two hours later the rabbits are sacrificed, synovial lavage is collected, and keratan sulfate (KS) and sulfated glycosaminoglycan (S-GAG) fragments released into the joint are quantitated. Keratan sulfate is measured by an inhibition ELISA using the method of Thonar (Thonar, E.J.-M.A., Lenz, M.E., Klinsworth, G.K., Caterson, B., Pachman, L.M., Glickman, P., Katz, R., Huff, J., Keuttner, K.E. Quantitation of keratan sulfate in blood as a marker of cartilage catabolism, Arthr. Rheum. 28, 1367-1376 (1985)). Sulfated glycosaminoglycans are measured by first digesting the synovial lavage with streptomyces hyaluronidase and then measuring DMB dye binding using the method of Goldberg (Goldberg, R.L. and Kolibas, L. An improved method for determining proteoglycan synthesized by chondrocytes in culture. Connect. Tiss. Res. 24,, 265-275 (1990)). For an i.v. study, a compound is solubilized in 1 ml of PEG-400, and for a p.o. study, a compound is administered in 5 ml of fortified corn starch per kilogram of body weight.

The compounds of formula I can be prepared e.g. by condensing a carboxylic acid of formula IV,



(IV)

or a reactive functional derivative thereof, wherein R, R_1, R_2 and Ar having meaning as defined in claim 1, with hydroxylamine of formula V,

NH_2-OH (V)

optionally in protected form, or a salt thereof;
and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, carboxyl and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, carboxyl and hydroxy groups are those that can be converted under mild conditions into free amino and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1991.

In the processes cited herein, reactive functional derivatives of carboxylic acids represent, for example, anhydrides especially mixed anhydrides, acid halides, acid azides, lower alkyl esters and activated esters thereof. Mixed anhydrides are preferably such from pivalic acid, or a lower alkyl (ethyl, isobutyl) hemiester of carbonic acid; acid halides are for example chlorides or bromides; activated esters for example succinimido, phthalimido or 4-nitrophenyl esters; lower alkyl esters are for example the methyl or ethyl esters.

Also, a reactive esterified derivative of an alcohol in any of the reactions cited herein represents said alcohol esterified by a strong acid, especially a strong inorganic acid, such as a hydrohalic acid, especially hydrochloric, hydrobromic or hydroiodic acid, or sulphuric acid, or by a strong organic acid, especially a strong organic sulfonic acid, such as an aliphatic or aromatic sulfonic acid, for example methanesulfonic acid, 4-methylbenzenesulfonic acid or 4-bromobenzenesulfonic acid. A said reactive esterified derivative is especially halo, for example chloro, bromo or iodo, or aliphatically or aromatically substituted sulfonyloxy, for example methanesulfonyloxy, 4-methylbenzenesulfonyloxy(tosyloxy).

In the above processes for the synthesis of compounds of the invention can be carried out according to methodology generally known in the art for the preparation of hydroxamic acids and derivatives thereof.

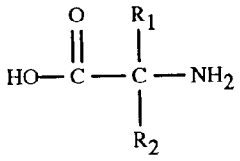
The synthesis according to the above process (involving the condensation of a free carboxylic acid of formula IV with an optionally hydroxy protected hydroxylamine derivative of formula V can be carried out in the presence of a condensing agent, e.g. 1,1'-carbonyldiimidazole, or N-(dimethylaminopropyl)-N'-ethylcarbodiimide or dicyclohexylcarbodiimide with or without 1-hydroxybenzotriazole in an inert polar solvent, such

as dimethylformamide or dichloromethane, preferably at room temperature.

The synthesis involving the condensation of a reactive functional derivative of an acid of formula IV as defined above, e.g. an acid chloride or mixed anhydride with optionally hydroxy protected hydroxylamine, or a salt thereof, in presence of a base such as triethylamine can be carried out, at a temperature ranging preferably from about -78 °C to +75 °C, in an inert organic solvent such as dichloromethane or toluene.

Protected forms of hydroxylamine (of formula V) in the above process are those wherein the hydroxy group is protected for example as a t-butyl ether, a benzyl ether or tetrahydropyranyl ether. Removal of said protecting groups is carried out according to methods well known in the art, e.g. hydrogenolysis or acid hydrolysis. Hydroxylamine is preferably generated in situ from a hydroxylamine salt, such as hydroxylamine hydrochloride.

The starting carboxylic acids of formula IV can be prepared as follows:
An amino acid of formula VI

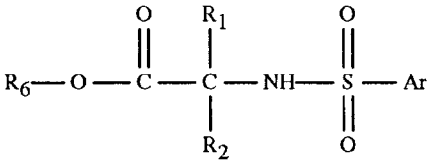


(VI)

wherein R_1 and R_2 have meaning as defined herein, is first esterified with a lower alkanol, e.g. methanol, in the presence of e.g. thionyl chloride to obtain an aminoester which is treated with a reactive functional derivative of the appropriate arylsulfonic acid of the formula VII

$ArSO_3H$ (VII)

wherein Ar has meaning as defined hereinabove, e.g. with the arylsulfonyl chloride, in the presence of a suitable base such as triethylamine using a polar solvent such as tetrahydrofuran, toluene, acetonitrile to obtain a compound of the formula VIII

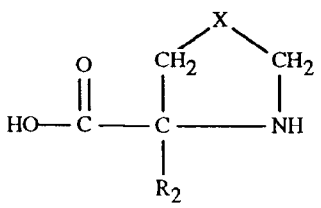


(VIII)

wherein R_1, R_2 and Ar have meaning as defined herein and R_6 is a protecting group, e.g. lower alkyl. Treatment thereof with a reactive esterified derivative of the alcohol of the formula IX

$R\text{-}CH_2OH$ (IX)

wherein R has meaning as defined herein, such as the halide, e.g. the chloride, bromide or iodide derivative thereof, in the presence of an appropriate base, such as potassium carbonate or sodium hydride, in a polar solvent such as dimethylformamide. The resulting compound corresponding to an ester of a compound of formula IV can then be hydrolyzed to the acid of formula IV, using standard mild methods of ester hydrolysis, preferably under acidic conditions. For compounds of formula Ia (wherein R and R_1 of formula I are combined) the starting materials are prepared by treating a carboxylic acid of formula X



(X)

or an ester thereof, wherein R_2 and X have meaning as defined above, with a reactive functional derivative of a compound of the formula $ArSO_3H$ (VII) under conditions described for the preparation of a compound of formula VIII.

The starting materials of formula VI, VII, IX and X are either known in the art, or can be prepared by methods well-known in the art or as described herein.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures (preferably at or near the boiling point of the solvents used), and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed in situ under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known per se.

The invention also relates to any novel starting materials and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, optical isomers (antipodes), racemates, or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. The hydroxamic acids or carboxylic acid intermediates can thus be resolved into their optical antipodes e.g. by fractional crystallization of d- or 1-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts.

Finally, acidic compounds of the invention are either obtained in the free form, or as a salt thereof.

Acidic compounds of the invention may be converted into salts with pharmaceutically acceptable bases, e.g. an aqueous alkali metal hydroxide, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g. diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit matrix-degrading metalloproteinases, and for the treatment of disorders responsive thereto, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbants, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspen-

sions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75 %, preferably about 1 to 50 %, of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art.

The pharmaceutical formulations contain an effective matrix-degrading metalloproteinase inhibiting amount of a compound of the invention as defined above either alone, or in combination with another therapeutic agent, e.g. an anti-inflammatory agent with cyclooxygenase inhibiting activity, each at an effective therapeutic dose as reported in the art. Such therapeutic agents are well-known in the art.

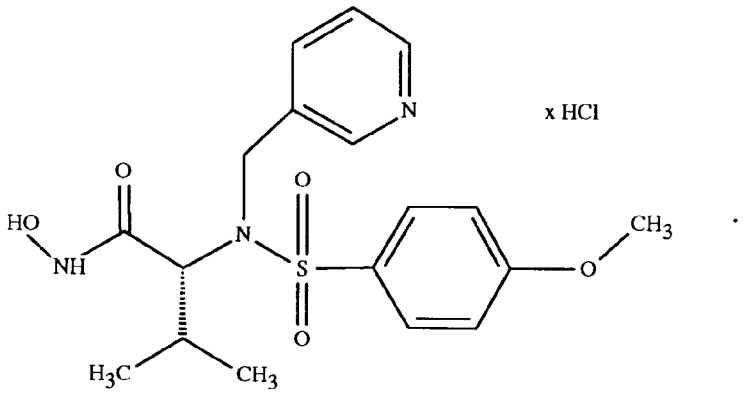
Examples of antiinflammatory agents with cyclooxygenase inhibiting activity are diclofenac sodium, naproxen, ibuprofen, and the like.

In conjunction with another active ingredient, a compound of the invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 25 and 250 mg of the active ingredient.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art.

Example 1: (a) N-(t-Butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide (4.1 g, 9.13 mmol) is dissolved in dichloroethane (150 mL) containing ethanol (0.53ml, 9.13 mmol) in a round bottom flask, and the reaction is cooled to -10 °C. Hydrochloric acid gas (from a lecture bottle) is bubbled through for 30 minutes. The reaction is sealed, allowed to slowly warm to room temperature, and stirred for 2 days. The solvent is reduced to 1/3 volume by evaporation and triturated with ether. The mixture is filtered, filter cake removed, and dried in vacuo to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride as a white solid, m.p. 169-170 °C (dec), and having the following structure:



The starting material is prepared as follows:

To a solution of D-valine (15.0 g, 128.0 mmol) in 1:1 dioxane/ water (200 mL) containing triethylamine (19.4 g, 192.0 mmol) at room temperature is added 4-methoxybenzenesulfonyl chloride (29.0 g, 141.0 mmol), and the reaction mixture is stirred at room temperature overnight. The mixture is then diluted with methylene chloride, washed with 1N aqueous hydrochloric acid and water. The organic layer is washed again with brine, dried (Na_2SO_4), and the solvent is evaporated to provide N-[4-methoxybenzenesulfonyl]-(D)-valine as a crude product. A solution of this crude product (15.0 g) in toluene (100 mL) containing N,N-dimethylformamide di-t-butyl acetal (50 mL, 206.5 mmol) is heated to 95 °C for 3 hours. The solvent is then evaporated. The crude product is purified by silica gel chromatography (30% ethyl acetate/hexanes) to provide N-[4-methoxybenzenesulfonyl]-(D)-valine t-butyl ester.

To a solution of N-[4-methoxybenzenesulfonyl]-(D)-valine t-butyl ester (4.38 g, 13.0 mmol) in dimethylformamide (200 mL) is added 3-picolyl chloride hydrochloride (2.3 g, 14.0 mmol) followed by potassium carbonate (17.94 g, 130.0 mmol). The reaction mixture is stirred at room temperature for 2 days. The mixture is then diluted with water and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (ethyl acetate) to give t-butyl 2(R)-[N-[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoate.

t-Butyl 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoate (5.3 g, 12.2 mmol) is dissolved in methylene chloride (150 mL) and cooled to -10 °C. Hydrochloric acid gas is bubbled into the solution for 10 minutes. The reaction mixture is then sealed, warmed to room temperature and stirred for 4 hours. The solvent is then evaporated to provide 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride.

2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride (5.0 g, 12.06 mmol), 1-hydroxybenzotriazole (1.63 g, 12.06 mmol), 4-methylmorpholine (6.6 mL, 60.31 mmol), and O-t-butylhydroxylamine hydrochloride (54.55 g, 36.19 mmol) are dissolved in methylene chloride (200 mL). N-[Dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (3.01 g, 15.68 mmol) is added, and the reaction is stirred overnight. The reaction is then diluted with water and extracted with methylene chloride.

The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (2% methanol/methylene chloride) to give N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide.

(b) L-tartaric acid salt, m.p. 114-116 °C.

(c) Methanesulfonic acid salt, m.p. 139-141.5 °C.

(d) Maleic acid salt, m.p. 133-134 °C.

Example 2: The following compounds are prepared similarly to Example 1:

a) N-Hydroxy-2(S)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride, m.p. 170.5-171 °C, by starting the synthesis with L-valine, and carrying out the subsequent steps as described above.

(b) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-4-methylpentanamide hydrochloride, m.p. 128-129 °C.

The first two steps are carried out as described in example 1, except the synthesis was started with D-leucine. The alkylation step is different, as described below.

To a solution of t-butyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-4-methylpentanoate (10.0 g, 27.92 mmol) in dimethylformamide (250 mL) at room temperature is added 3-picolyl chloride hydrochloride (4.81 g, 29.32 mmol) followed by sodium hydride (2.79 g, 69.80 mmol, 60% in oil). The reaction mixture is stirred at room temperature for 48 hours. The mixture is quenched with water and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2S0_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (45% ethyl acetate/hexanes) to provide t-butyl 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-4-methylpentanoate.

All of the following steps are carried out as described above in example 1.

(c) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino]-4-methylpentanamide, m.p. 85-87 °C, by starting the synthesis with D-leucine and alkylating with 6-chloropiperonyl chloride (=6-chloro-3,4-methylenedioxy-benzylchloride) in the third step.

(d) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](piperonyl)amino]-4-methylpentanamide, m.p. 145-147 °C, by starting the synthesis with D-leucine and alkylating with piperonyl chloride (=3,4-methylenedioxy-benzylchloride) in the third step.

(e) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-4-methylpentanamide, m.p. 89-90 °C, by starting the synthesis with D-leucine and alkylating with 2-picolyl chloride in the third step.

(f) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-3-methylbutanamide hydrochloride, m.p. 140-142 °C, by starting the synthesis with D-valine and alkylating with 2-picolyl chloride in the third step.

(g) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-4,4-dimethylpentanamide hydrochloride, m.p. 130-150 °C (slow melt), by starting the synthesis with D-t-butylalanine and alkylating with 3-picolyl chloride in the third step.

(h) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-cyclohexylacetamide hydrochloride, m.p. 149.5-152.0 °C, by starting the synthesis with (D)-cyclohexylglycine hydrochloride.

The starting amino acid is prepared as follows:

(D)-phenylglycine (10.0 g, 66.2 mmol) is suspended in 2N hydrochloric acid (100 mL) containing platinum (IV) oxide hydrate (267 mg). The mixture is shaken in a Parr hydrogenation apparatus for 24 hours under a hydrogen pressure of 50 psi. The resultant suspended crystalline material, (D)-cyclohexylglycine hydrochloride, was used without further purification.

(i) N-Hydroxy-2(R)-[[(2,3-dihydrobenzofuran)-5-sulfonyl](3-picolyl)amino]3-methylbutanamide hydrochloride, m.p. 150.0-153.0 °C, by starting the synthesis with 2,3-dihydrobenzofuran-5-sulfonyl chloride.

The starting sulfonyl chloride is prepared as follows:

2,3-dihydrobenzofuran (6.0 g, 49.94 mmol) is added over 20 minutes to chlorosulfonic acid (29.09 g, 249.69 mmol) at -20 °C. The reaction mixture is quenched by addition of ice followed by water (20 mL). The mixture is then extracted with ethyl acetate. The combined organic estracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (30% ethyl acetate/hexane) to give 2,3-dihydrobenzofuran-5-sulfonyl chloride (3.3 g).

(j) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-m ethylbutanamide hydrochloride, m.p. 139.5-142 °C, by starting the synthesis with DL-valine.

(k) N-Hydroxy-2(R)-[[4-ethoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide hydrochloride, $[\alpha]_D^{25} = +34.35$ (c = 5.84, CH_3OH).

(l) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-cyclohexylacetamide hydrochloride, m.p. 127-140 °, by starting the syntheses with (D)-cyclohexylglycine hydrochloride, and carrying out the subsequent steps as described above.

(m) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-cyclohexylacetamide hydrochloride, m.p. 137-139 °C, using 4-chloromethyl-2-methylthiazole in the alkylation step.

(n) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]-2-cyclohexylacetamide hydrochloride, m.p. 121-123 °C, using 2-chloromethylquinoline hydrochloride in the alkylation step.

Example 3: 2(R)-[[4-Methoxybenzenesulfonyl](benzyl)amino]-4-methylpentanoic acid (4.38 g, 11.2 mmol) is dissolved in methylene chloride (56.0 mL). To this solution is added oxalyl chloride (1.95 mL, 22.4 mmol) and dimethylformamide (0.86 mL, 11.2 mmol), and the reaction is stirred at room temperature for 90 minutes. Meanwhile, in a separate flask, hydroxylamine hydrochloride (3.11 g, 44.8 mmol) and triethylamine (9.36 mL, 67.1 mmol) are stirred in tetrahydrofuran (50.0 mL) and water (3.5 mL) at 0 °C for 15 minutes. After 90 minutes, the methylene chloride solution is added in one portion to the second flask, and the combined contents are stirred for three days as the flask gradually warms up to room temperature. The reaction is then diluted with acidic water (pH = ~3), and extracted several times with ethyl acetate. The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (1% methanol/methylene chloride) to give N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-methylpentanamide, m.p. 48-52 °C.

The starting material is prepared as follows:

(D)-leucine (7.1 g, 53.9 mmol) is dissolved in dioxane (60.0 mL) and water (60.0 mL). To this solution is added triethylamine (11.3 mL, 80.9 mmol) and 4-methoxybenzenesulfonyl chloride (12.25 g, 59.3 mmol), and the reaction is stirred at room temperature overnight. The reaction is then diluted with methylene chloride and washed successively with 2.5N hydrochloric acid, water, and brine. The organic phase is dried (Na_2SO_4), and the solvent is evaporated to give N-[4-methoxybenzenesulfonyl]-(D)-leucine, which is used without further purification.

N-[4-methoxybenzenesulfonyl]-(D)-leucine (14.0 g, 46.5 mmol) is dissolved in toluene (100.0 mL), and heated to 90 °C. N,N-Dimethylformamide di-t-butyl acetal (45.0 mL, 186.0 mmol) is added dropwise over 20 minutes, and then the reaction is kept at 90 °C for another 2 hours. After cooling back down, the reaction is diluted with ethyl acetate and washed successively with saturated sodium bicarbonate, water, and brine. The organic phase is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (20% ethyl acetate/ hexane) to give N-[4-methoxybenzenesulfonyl]-(D)-leucine t-butyl ester.

To a suspension of sodium hydride (0.68 g, 14.1 mmol) in dimethylformamide (60.0 mL), is added N-[4-methoxybenzenesulfonyl]-(D)-leucine t-butyl ester (5.02 g, 14.06 mmol) in dimethylformamide (10.0 mL). After stirring at room temperature for 20 minutes, benzyl bromide (1.67 mL, 14.06 mmol) is added, and the reaction is stirred overnight at room temperature. The reaction is then partitioned between ethyl acetate and acidic water (pH = 5), the organic layer is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (10% ethyl acetate/hexane) to give t-butyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-methylpentanoate.

t-Butyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-methylpentan oate (5.38 g, 12.02 mmol) is dissolved in methylene chloride (100.0 mL). Hydrochloric acid gas (from a lecture bottle) is bubbled through the solution for 20 minutes. The reaction is sealed and stirred overnight at room temperature. The solvent is then evaporated to give 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-methylpentanoic acid.

Example 4: The following compounds are prepared similarly to example 3:

(a) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-phenylacetamide, m.p. 128-129 °C, by starting the synthesis with (D)-phenylglycine, and carrying out the subsequent steps as described in example 3.

(b) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-t-butylacetamide, m.p. 69-73 °C, by starting the synthesis with t-butylglycine, and carrying out the subsequent steps as described in example 3.

(c) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]-4-methylpentanamide, m.p. 48-51 °C, by starting the synthesis with (D)-leucine, and carrying out the subsequent steps as described in example 3, with the exception that 4-fluorobenzyl bromide is used in place of benzyl bromide.

(d) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-3-methylbutanamide, m.p. 179-180 °C, by starting the synthesis with (D)-valine, and carrying out the subsequent steps as described in example 3.

(e) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4,4-dimethylpentanamide, by starting the synthesis with (D)-neopentylglycine, and carrying out the subsequent steps as described in example 3.

(f) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl(benzyl)amino]-3-hydroxypropanamide, m.p. 65 °, by starting the synthesis with (D)-serine, and carrying out the subsequent steps as described in example 3.

Example 5: 3-[4-Methoxybenzenesulfonyl]-5,5-dimethylthiazolidine-4(S)-carboxylic acid (2.0 g, 6.0 mmol) is dissolved in methylene chloride (30.0 mL). To this solution is added oxalyl chloride (1.1 mL, 12.1 mmol) and dimethylformamide (0.50 mL, 6.0 mmol), and the reaction is stirred at room temperature for 2 hours. Meanwhile, in a separate flask, hydroxylamine hydrochloride (1.74 g, 25.0 mmol) and triethylamine (5.0 mL, 36.0 mmol) are stirred in tetrahydrofuran (25.0 mL) and water (2.0 mL) at 0 °C for 15 minutes. After 2 hours, the methylene chloride solution is added in one portion to the second flask, and the combined contents are stirred overnight as the flask gradually warms up to room temperature. The reaction is then diluted with acidic water (pH = ~3), and extracted several times with ethyl acetate. The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (60% ethyl acetate/hexane) to give N-hydroxy-3-[4-methoxybenzenesulfonyl]-5,5-dimethylthiazolidine-4(S)-carboxamide, m.p. 68-71 °C.

The starting material is prepared as follows:

(D)-5,5-Dimethylthiazolidine-4-carboxylic acid (1.0 g, 6.2 mmol) is dissolved in dioxane (10.0 mL) and water (10.0 mL). To this solution is added triethylamine (1.3 mL, 9.3 mmol) and 4-methoxybenzenesulfonyl chloride (1.41 g, 6.82 mmol), and the reaction is stirred at room temperature for three days. The reaction is then diluted with ethyl acetate and washed successively with 2.5N hydrochloric acid, water, and brine. The organic phase is dried (Na_2SO_4), and the solvent is evaporated to give 3-[4-methoxybenzenesulfonyl]-5,5-dimethylthiazolidine-4(S)-carboxylic acid, which is used without further purification.

Example 6: 1-[4-Methoxybenzenesulfonyl]-pyrrolidine-2(R)-carboxylic acid (1.12 g, 3.93 mmol) is dissolved in methylene chloride (40.0 mL). To this solution is added oxalyl chloride (0.69 mL, 7.85 mmol) and dimethylformamide (0.30 mL, 3.93 mmol), and the reaction is stirred at room temperature for 30 minutes. Meanwhile, in a separate flask, hydroxylamine hydrochloride (1.1 g, 15.7 mmol) and triethylamine (3.3 mL, 23.5 mmol) are stirred in tetrahydrofuran (20.0 mL) and water (4.0 mL) at 0 °C for 15 minutes. After 30 minutes, the methylene chloride solution is added in one portion to the second flask, and the combined contents are stirred overnight as the flask gradually warms up to room temperature. The reaction is then diluted with acidic water (pH = ~3), and extracted several times with ethyl acetate. The combined organic layers are dried ($MgSO_4$), and the solvent is evaporated. The product is purified by silica gel chromatography (50% ethyl acetate/hexane) to give N-hydroxy-1-[4-methoxybenzenesulfonyl]-pyrrolidine-2(S)-carboxamide, m.p. 163.5-165.5 °C.

The starting material is prepared as follows:

(D)-proline (0.78g, 6.77 mmol) is suspended in methylene chloride (25.0 mL). To this solution is added

triethylamine (1.13 mL, 8.12 mmol) and 4-methoxybenzenesulfonyl chloride (1.4 g, 6.77 mmol), and the reaction is stirred at room temperature for two days. The reaction is then diluted with methylene chloride and washed successively with 1N hydrochloric acid, water, and brine. The organic phase is dried ($MgSO_4$), and the solvent is evaporated. The product is purified by silica gel chromatography (10% methanol/ethyl acetate) to give 1-[4-methoxybenzenesulfonyl]-pyrrolidine-2(R)-carboxylic acid.

Example 7: N-(t-Butyloxy)-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]-acetamide (2.65 g, 5.1 mmol) is dissolved in methylene chloride (30.0 mL) and ethanol (1.0 mL) in a glass sealed tube, and the reaction is cooled to 0 °C. Hydrochloric acid gas (from a lecture bottle) is bubbled through the solution for 20 minutes, and then the tube is sealed and kept at room temperature for 3 days. After that time, the solvent is removed, and the reaction is partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (2% methanol/methylene chloride) to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]acetamide m.p. 56-60 °C.

The starting material is prepared as follows:

N-(2-chloroethyl)morpholine hydrochloride (12.0 g) is dissolved in water (200 mL) and made basic with ammonium hydroxide (100.0 mL) to a pH = ~11. The aqueous layer is then extracted several times with ether, the combined organic layers are dried (Na_2S0_4), and the solvent is evaporated to yield an oil which is used immediately.

Diethyl acetamidomalonate (11.4 g, 57.08 mmol) is added to a freshly prepared solution of sodium ethoxide in ethanol (made from Na (1.32 g, 57.1 mmol) added to ethanol (34.0 mL)), and the reaction is refluxed for 30 minutes. The reaction is then adjusted to 55 °C, and potassium iodide (0.14 g, 0.8 mmol) and dimethylformamide (0.2 mL) are added. Finally, the N-(2-chloroethyl)morpholine (8.9 g, 59.6 mmol) prepared above is added in ethanol (14.0 mL), and the reaction is maintained at 55 °C for 24 hours.

The reaction is diluted with ethyl acetate and filtered through Celite to remove salts. The filtrate is evaporated, and then partitioned between ethyl acetate and brine. The organic layer is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (first 50% ethyl/acetate, then 5% methanol/methylene chloride) to give diethyl [2-(4-morpholino)ethyl]acetamidomalonate.

Diethyl [2-(4-morpholino)ethyl]acetamidomalonate (8.0 g, 25.6 mmol) is dissolved in ethanol (128.0 mL). Sodium hydroxide (4.55 mL of a 6N aqueous solution, 27.35 mmol) is added, and the reaction is stirred at room temperature for 24 hours. The ethanol is then evaporated, and the residue is diluted up in water, washed several times with ether, and then the aqueous phase is acidified with concentrated hydrochloric acid to pH = ~5. The solution is evaporated to dryness, then suspended in toluene (300.0 mL) and refluxed for 3 hours. After cooling to room temperature, the reaction is diluted with chloroform (300.0 mL), and the mixture is filtered through Celite. The filtrate is evaporated to give ethyl 2-(acetamido)-2-[2-(4-morpholino)-ethyl]acetate.

Ethyl 2-(acetamido)-2-[2-(4-morpholino)ethyl]acetate (4.2 g, 16.28 mmol) is dissolved in 6N hydrochloric acid (100.0 mL), and the reaction is refluxed for 4.5 hours. The water is then evaporated, and the product is azeotroped dry using toluene to give 2-amino-2-[2-(4-morpholino)ethyl]acetic acid dihydrochloride.

2-Amino-2-[2-(4-morpholino)ethyl]acetic acid dihydrochloride (4.0 g, 15.33 mmol) is dissolved in a solution of methanol (100.0 mL) and acetyl chloride (5.0 mL), and the reaction is refluxed for 24 hours. The solvent is then evaporated to give methyl 2-amino-2-[2-(4-morpholino)ethyl]acetate dihydrochloride.

Methyl 2-amino-2-[2-(4-morpholino)ethyl]acetate dihydrochloride (6.0 g, 21.82 mmol) is dissolved in chloroform (110.0 mL) and triethylamine (9.12 mL, 65.46 mmol). To this solution is added 4-methoxybenzenesulfonyl chloride (4.51 g, 21.82 mmol), and the reaction is refluxed for 4 hours. After cooling, the reaction is diluted with more chloroform, washed with saturated sodium bicarbonate, the organic layer is dried (Na_2SO_4), and the solvent is evaporated to give methyl 2-(4-methoxybenzenesulfonyl)amino-2-[2-(4-morpholino)ethyl]acetate.

To a suspension of sodium hydride (1.03 g, 21.5 mmol) in dimethylformamide (108.0 mL), is added methyl 2-(4-methoxybenzenesulfonyl)amino-2-[2-(4-morpholino)ethyl]ac etate (8.0 g, 21.5 mmol) in dimethylformamide (10.0 mL). After stirring at room temperature for 30 minutes, benzyl bromide (2.56 mL, 21.5 mmol) is added, and the reaction is stirred overnight at room temperature. The reaction is then partitioned between ethyl acetate and acidic water (pH = ~5), the organic layer is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (3% methanol/methylene chloride) to give methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]acetate.

Methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholin o)ethyl]acetate (7.33 g, 15.86 mmol) is dissolved in methanol (80.0 mL). To this solution is added sodium hydroxide (17.5 mL of a 1N aqueous solution, 17.5 mmol), and the reaction is stirred at room temperature for 8 hours. The reaction is then acidified to pH = ~3 using 2.5N hydrochloric acid, and then the solvent is evaporated. The residue is

suspended in ethanol, the inorganic salts are filtered away, and the filtrate is evaporated to give 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]acetic acid hydrochloride.

2-[[4-Methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]acetic acid hydrochloride (4.24 g, 8.75 mmol), 1-hydroxybenzotriazole (1.34 g, 8.75 mmol), 4-methylmorpholine (3.85 mL, 35.02 mmol), and O-t-butylhydroxylamine hydrochloride (1.10 g, 8.75 mmol) are dissolved in methylene chloride (44.0 mL), and the reaction is cooled to 0 °C. To this solution is added N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (3.35 g, 17.5 mmol), and the reaction is allowed to warm up to room temperature and stir overnight. The reaction is diluted with more methylene chloride, and the organic layer is washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent is evaporated. The product is purified by silica gel chromatography (2% methanol/methylene chloride) to give N-(t-butyloxy)-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]acetamide.

Example 8: The following compounds are prepared similarly to example 7:

(a) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]-2-[2-(4-morpholino)ethyl]acetamide, m.p. 62-64 °C, using isobutyl bromide in the alkylation step in place of benzyl bromide.

(b) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride, m.p. 195-197 °C, using 2-picolyl chloride in the alkylation step in place of benzyl bromide.

(c) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride, m.p. >210 °C, using 3-picolyl chloride in the alkylation step in place of benzyl bromide.

(d) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-[2-(4-morpholino)-ethyl]acetamide dihydrochloride, m.p. 180 °C, using 4-chloromethyl-2-methylthiazole in the alkylation step in place of benzyl bromide.

(e) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-thiomorpholino)ethyl]acetamide, m.p. 50-52 °C, by starting the synthesis with N-(2-chloroethyl)thiomorpholine,and carrying out the subsequent steps as described in example 7.

(f) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-methylthiazol-4-ylmethyl]acetamide m.p. 79-81 °C, by starting the synthesis with 4-chloromethyl-2-methylthiazole hydrochloride, and carrying out the subsequent steps as described in example 7.

(g) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[6-chloropiperonyl]acetamide, m.p. 70-74 °C, by starting the synthesis with 6-chloropiperonyl chloride, and carrying out the subsequent steps as described in example 7.

(h) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-pyrazolyl)methyl]acetamide, m.p. 130-131 °C, by starting the synthesis with β-pyrazol-1-yl-alanine (prepared following the procedure of J. Am. Chem. Soc., 110, p. 2237 (1988)), and carrying out the subsequent steps as described in example 7.

(i) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[3-picolyl]acetamide dihydrochloride, m.p. >220 °C, by starting the synthesis with 3-picolyl chloride, and carrying out the subsequent steps as described in example 7, but in addition, using 3-picolyl chloride in the alkylation step in place of benzyl bromide in example 7.

(j) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride, m.p. >200 °C, by starting the synthesis with N-τ-methylhistidine dihydrochloride (prepared following the procedure of Recueil, 97, p.293 (1978)), and carrying out the subsequent steps as described in example 7.

(k) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride, m.p. 194-195 °C, by starting the synthesis with N-τ-methylhistidine dihydrochloride and carrying out the subsequent steps as described in example 7, using isobutyl iodide in the alkylation step in place of benzyl bromide.

(l) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride, m.p. >220 °C, by starting the synthesis with N-τ-methylhistidine dihydrochloride and carrying out the subsequent steps as described in example 7, using 3-picolyl chloride in the alkylation step in place of benzyl bromide.

(m) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]-acetamide hydrochloride, m.p. 162-164 °C, by starting the synthesis with N-τ-methylhistidine dihydrochloride and carrying out the subsequent steps as described in example 7, using 2-picolyl chloride in the alkylation step in place of benzyl bromide.

(n) N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride, m.p. 160-163 °C, by starting the synthesis with N-τ-methylhistidine dihydrochloride and carrying out the subsequent steps as described in example 7, using 4-chloromethyl-2-methylthiazole in the alkylation step in place of benzyl bromide.

(o) N-hydroxy-2-[[4-methoxybenzenesulfonyl](piperonyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]-acetamide hydrochloride, m.p. 195 °C, by starting the synthesis with N-τ-methylhistidine dihydrochloride and carrying out the subsequent steps as described in example 7, using piperonyl chloride in the alkylation step in place of benzyl bromide.

Example 9: (a) Methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]propionate (2.1 g, 6.01 mmol) is dissolved in methanol (20.0 mL). To this solution is added hydroxylamine hydrochloride (0.84 g, 12.0 mmol), followed by the addition of sodium methoxide (7.0 mL of a 4.37M solution). The reaction is stirred overnight at room temperature. The reaction is worked up by first removing all the solvent, and partitioning between ethyl acetate/hexane (2/1) and saturated sodium bicarbonate. The aqueous phase is extracted well with ethyl acetate/hexane, the combined organic layers are dried ($MgSO_4$), and the solvent is evaporated. The product is purified by silica gel chromatography (ethyl acetate) to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]propionamide, m.p. 149-151 °C.

The starting material is prepared as follows:

D,L-Alanine (27.0 g, 300.0 mmol) is dissolved in a solution of methanol (100.0 mL) saturated with HCl gas, and the reaction is refluxed for 2 hours. The solvent is then evaporated, and the residue triturated with ethyl acetate to give alanine methyl ester hydrochloride.

Alanine methyl ester hydrochloride (7.0 g, 50.0 mmol) is dissolved in methylene chloride (100.0 mL) and triethylamine (20.0 mL, 143.0 mmol). To this solution is added 4-methoxybenzenesulfonyl chloride (10.3 g, 50.0 mmol), and the reaction is stirred at room temperature briefly. The reaction is made basic with 1N sodium hydroxide, and washed with methylene chloride. The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. Hexane is added to the residue and the precipitate is collected to give N-[4-methoxybenzenesulfonyl]-alanine methyl ester.

To a suspension of sodium hydride (0.60 g, 11.0 mmol) in dimethylformamide (20.0 mL), is added N-[4-methoxybenzenesulfonyl]-alanine methyl ester (2.6 g, 10.0 mmol) in dimethylformamide (10.0 mL). After stirring at room temperature for 30 minutes, benzyl bromide (1.22 mL, 10.0 mmol) is added, and the reaction is stirred for two hours at room temperature. The reaction is then partitioned between ether and brine, the organic layer is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (20% ether/hexanes) to give methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-propionoate.

(b) Similarly prepared is N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-thiomethyl-butyramide, m.p. 104-106 °C, by starting the synthesis with D,L-methionine, and carrying out the subsequent steps as described above.

Example 10: A solution of methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-(methylsulfonyl)-butyrate (900 mg, 2.0 mmol), sodium methoxide previously generated from sodium metal spheres (100.0 mg, 4.5 mmol), and hydroxylamine hydrochloride (280.0 mg, 4.0 mmol) is refluxed for 2 days. The mixture is cooled to room temperature, concentrated in vacuo, diluted with water, acidified with citric acid, and extracted with ethyl acetate. The combined organic extracts are dried ($MgSO_4$) and and the solvent is evaporated. The product is purified by silica gel chromatography (ethyl acetate) to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-(methylsulfonyl)butyramide, [M + 1] = 157.

The starting material is prepared as follows:

To a solution of racemic methionine methyl ester (1.98 g, 10.0 mmol) in methylene chloride (25 mL) containing triethylamine (2.0 mL, 14.3 mmol) is added 4-methoxybenzenesulfonyl chloride (2.1 g, 10.2 mmol). After stirring for 2 hours at room temperature, the mixture is diluted with 1 N hydrochloric acid. The organic layer is removed and the aqueous layer is extracted with ether. The combined organic layers are washed with brine, dried ($MgS0_4$), and and the solvent is evaporated. The concentrated solution is triturated with ether, and the product is collected by filtration to give methyl 2-[[4-methoxybenzenesulfonyl]amino]-4-(thiomethyl)butyrate.

To a solution of methyl 2-[[4-methoxybenzenesulfonyl]amino]-4-(thiomethyl)butyrate (2.1 g, 6.2 mmol) in dimethylformamide (15 mL) containing potassium carbonate (4.0 g, 29.0 mmol) is added benzyl bromide (1.5 mL, 12.6 mmol). The reaction mixture is stirred for 1 hour at room temperature. The mixture is quenched with water and extracted with ether. The organic extracts are washed with brine, dried ($MgS0_4$), and and the solvent is evaporated. The product is purified by silica gel chromatography (30% ethyl acetate/hexanes) to give methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-(thiomethyl)butyrate.

A solution of methyl 2-[[4-methoxybenzenesulfonyl](benzyl) amino]-4-(thiomethyl)butyrate (925.0 mg, 2.17 mmol) in 25% peracetic acid (5 mL) is stirred overnight at room temperature. The mixture is concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The combined organic extracts are dried ($MgSO_4$) and the solvent is evaporated to give methyl 2-[[4-methoxybenzenesulfonyl](benzyl)-amino]-4-(methylsulfonyl)butyrate.

Example 11: (a) To a solution of 2R-[[(4-methoxybenzene)sulfonyl](benzyl)amino]-propionic acid (1.04 g, 2.98 mmol) in methylene chloride (50 mL) containing dimethylformamide (230 mL, 2.98 mmol) at room temperature is added oxalyl chloride (520 mL, 5.96 mmol) over 5 minutes dropwise. The mixture is stirred for 30 minutes at room temperature, then added to a pre-formed mixture of hydroxylamine hydrochloride (828 mg, 11.92 mmol) and triethylamine (2.5 mL, 17.9 mmol) in tetrohydrofuran (20 mL)/water (1.5 mL) at 0 °C. The reaction mixture is stirred for 45 minutes at 0 °C then slowly warmed to room temperature for 15.5 hours. The mixture is acidified with 1N hydrochloric acid and extracted with methylene chloride. The combined organic extracts are washed with brine, dried ($MgSO_4$), and the solvent is evaporated. The crude product is recrystallized from diethyl ether/ethyl acetate (1:1) to give N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-propionamide, m.p. 127-129 °C.

The starting material is prepared as follows:

To a solution of D-alanine methyl ester hydrochloride (3.0 g, 21.5 mmol) in methanol (10 mL) is added benzaldehyde (2.3 mL, 22.6 mmol). The reaction mixture is stirred at room temperature for 3 hours. The solvent is then evaporated. To the resultant residue is added acetic acid (15 mL) and methanol (1 mL) followed by portionwise addition of sodium cyanoborohydride (1.35 g, 21.5 mmol) at room temperature. The mixture is stirred overnight, and then the solvent is evaporated. The remaining residue is diluted with water (75 mL) and basified with Na_2CO_3. The mixture is extracted with ethyl acetate (3x75 mL). The combined organic extracts are washed with brine (50 mL), dried (Na_2SO_4), and the solvent is evaporated to give N-benzyl-D-alanine methyl ester.

To a solution of N-benzyl-D-alanine methyl ester (~2 g) in methylene chloride (40 mL) containing triethylamine (2.47 mL, 17.7 mmol) is added 4-methoxybenzenesulfonyl chloride (2.44 g, 11.8 mmol). The reaction mixture is stirred overnight at room temperature. The mixture is acidified with 1N HCl and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (10%->20% ethyl acetate/hexanes) to provide methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino] propionate.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino] propionate (1.05 g, 2.89 mmol) in tetrahydrofuran (60 mL) at room temperature is added 1N aqueous sodium hydroxide (8.6 mL, 8.67 mmol). The reaction mixture is stirred for 19 hours at room temperature. The tetrahydrofuran is then evaporated. The remaining residue is acidified with 1N hydrochloric acid and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated to give 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino] propionic acid.

(b) Similarly prepared is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-benzylacetamide, [M + 1] = 441, by starting with (R)-phenylalanine, and carrying out the previously described steps.

Example 12: (a) To a solution of N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl(benzyl)amino]-6-(N,N-dimethylamino)-hexamide (2.13 g, 4.21 mmol) in 1,2-dichloroethane (140 mL) is added ethanol (250 mL, 4.21 mmol). The solution is cooled to -10 °C and hydrogen chloride gas is bubbled in for 30 minutes. The reaction mixture is then sealed and allowed to warm to room temperature, stirring for 2 days. At this time point, the reaction mixture is cooled to -10 °C and hydrogen chloride gas is bubbled in for an additional 30 minutes. The reaction mixture is sealed, warmed to room temperature, and stirred for 24 hours. The mixture is reduced in volume by 1/2 in vacuo and triturated with ether. The mother liquid is removed and the remaining white solid is dried in vacuo to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)-amino]-6-(N,N-dimethylamino)-hexanamide hydrochloride salt, m.p. 175-177 °C.

The starting material is prepared as follows:

To a solution of ϵ-N-CBZ-(R)-lysine methylester hydrochloride (15.0 g, 45.10 mmol) in methylene chloride (250 mL) containing triethylamine (15.72 mL, 112.75 mmol) is added 4- methoxybenzenesulfonyl chloride (10.25 g, 49.61 mmol) at 0 °C. The reaction mixture is warmed to room temperature and stirred overnight. The reaction mixture is diluted with methylene chloride and washed with 1 N hydrochloric acid. The organic layer is washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield a yellow oil. The product is purified by silica gel chromatography (50% ethyl acetate/hexanes) to give methyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-6-(N-benzylcarbamoyl) hexanoate.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-6-(N-benzylcarbamoyl) hexanoate (12.4 g, 26.5 mmol) in dimethylformamide (100 mL) is added potassium carbonate (7.5 g, 52 mmol) and benzyl bromide (3.3 mL, 28.0 mmol), and the reaction is stirred for 24 hours at room temperature. The mixture is partitioned between water and 50% diethyl ether/ethyl acetate. The aqueous layer is removed and extracted with 50% diethyl ether/ethyl acetate. The combined organic layers are washed with brine, dried ($MgSO_4$) and the solvent is evaporated. The crude product is purified by silica gel chromatography (50% ethyl acetate/hexanes) to give methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(N-benzylcarbamoyl) hexanoate.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(benzylcarbamoyl) hexanoate (8.61 g, 15.53 mmol) in 95% ethanol (150 mL) is added 1N hydrochloric acid (15.5 mL, 15.53 mmol) followed by 10% Pd/C (4.0 g). The reaction mixture is stirred at room temperature under 1 atmosphere of hydrogen gas for 2 hours. The mixture is filtered through Celite and the solvent is evaporated to provide methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-aminohexanoate.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-aminohexanoate (5.05 g, 12.02 mmol) in refluxing formic acid (120 mL) containing sodium formate (2.45 g, 36.07 mmol) is added 37% aqueous formaldehyde (2.70 mL, 36.07 mmol). While continuing to reflux the reaction mixture, three more aliquots of 37% aqueous formaldehyde (2.70 mL, 36.07 mmol each aliquot) are added at 10 minute intervals. The mixture is concentrated in vacuo to yield a yellow oil. The crude product is purified by silica gel chromatography (10:1:0.5; ethylacetate/methanol/ammonium hydroxide) to provide methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(N,N-dimethylamino) hexanoate. This procedure is repeated and the combined product is used in the next reaction.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(N,N-dimethylamino) hexanoate (4.55 g, 10.7 mmol) in tetrahydrofuran (100 mL) is added 1N aqueous lithium hydroxide (20 mL, 20.33 mmol). The reaction mixture is stirred at room temperature overnight. The reaction mixture is directly concentrated to dryness in vacuo to give the lithium salt of 2(R)-[[4-methoxybenzenesulfonyl](benzyl)-amino]-6-(N,N-dimethylamino) hexanoic acid.

To a solution of 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(N,N-dimethylamino) hexanoic acid lithium salt (4.42 g, 10.18 mmol) in methylene chloride (100 mL) containing N- methylmorpholine (6.73 mL, 61.06 mmol), 1-hydroxybenzotriazole monohydrate (1.64 g, 10.687 mmol) and O-t-butylhydroxyl amine hydrochloride (1.41 g, 11.20 mmol) is added N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (3.90 g, 20.36 mmol) at 0 °C. The reaction mixture is allowed to warm to room temperature and stirring is continued overnight. The mixture is diluted with methylene chloride, washed with saturated sodium bicarbonate, then with brine, dried (Na_2SO_4) and the solvent is evaporated. The crude product is purified by silica gel chromatography (10:1:0.5 ethyl acetate/methanol/ammonium hydroxide) to provide N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-(N,N-dimethylamino) hexanamide.

(b) Similarly prepared is N-hydroxy-2-(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-6-(N,N-dimethylamino)-hexanamide dihydrochloride, m.p. 179-180 °C.

The first step is carried out as described above. The alkylation step is carried out as follows:

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-6-(benzylcarbamoyl)-hexanoate (10.48 g, 22.43 mmol) in dimethylformamide (220 mL) at 0 °C is added 3-picolyl chloride hydrochloride (3.86 g, 23.55 mmol) followed by sodium hydride (2.24 g, 56.07 mmol, 60% in oil). The reaction mixture is warmed to room temperature and stirred for 24 hours. The reaction mixture is quenched with water and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2S0_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (75% ethyl acetate/hexanes) to provide methyl 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-6-(benzylcarbamoyl) hexanoate.

All of the following steps are carried out as described above.

(c) Similarly prepared is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-6-(N,N-dimethylamino)-hexanamide dihydrochloride, m.p. 134-136 °C, by alkylating with 2-picolyl chloride in the second step and carrying out the subsequent steps as described above.

Example 13: N-(t-Butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)-amino] hexanamide (2.17 g, 3.86 mmol) is dissolved in dichloroethane (12 mL) containing ethanol (0.22 mL, 3.86 mmol), and the reaction is cooled to -10 °C. Hydrochloric acid gas is bubbled through this solution for 30 minutes. The reaction is sealed, warmed to room temperature and stirred for 2 days. The solvent is reduced to 1/2 volume by evaporating solvent, and triturated with ether. The resulting solid is removed and dried in vacuo to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanamide hydrochloride, m.p. 105-108 °C.

The starting material is prepared as follows:

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-amino hexanoate hydrochloride (7.5 g, 16.44 mmol) in methylene chloride (170 mL) is added 1-hydroxybenzotriazole monohydrate (2.64 g, 1726 mmol), N-methylmorpholine (5.44 mL, 49.34 mmol), and N,N-dimethylglycine (1.86 g, 18.08 mmol), and the reaction is coled to 0 °C. N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (6.30 g, 32.88 mmol) is added at 0 °C. The reaction mixture is warmed to room temperature and stirred overnight. The mixture is diluted with methylene chloride and washed with saturated aqueous sodium bicarbonate, and then with brine. The organic layer is dried (Na_2SO_4), filtered, and and the solvent is evaporated. The crude product is purified by silica gel chromatography (10/0.5/0.5 ethyl acetate/methanol/ammonium hydroxide) to

provide methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanoate (6.04 g).

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanoate (3.95 g, 7.82 mmol) in tetrahydrofuran (75 mL) at 0 °C is added 1N lithium hydroxide (15.64 ml, 15.64 mmol). The reaction mixture is warmed to room temperature and stirred overnight. The tetrahydrofuran is removed and the remaining aqueous layer is acidified with 1N hydrochloric acid. The mixture is evaporated to dryness to yield 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanoic acid hydrochloride.

To a solution of 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanoic acid hydrochloride (4.12 g, 7.82 mmol) in methylene chloride (78 mL) and dimethylformamide (5 mL) is added 1-hydroxybenzotriazole monohydrate (1.26 g, 8.21 mmol), N-methylmorpholine (2.58 ml, 23.45 mmol), and O-t-butyhydroxylamine hydrochloride (1.08 g, 8.60 mmol). The reaction is cooled to 0 °C, and N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (3.0 g, 15.64 mmol) is added. The reaction mixture is warmed to room temperature and stirred overnight. The mixture is then diluted with methylene chloride and washed with saturated aqueous sodium bicarbonate, and then with brine. The organic layer is dried (Na_2SO_4), filtered, and and the solvent is evaporated. The crude product is purified by silica gel chromatography (10/0.5/0.5 ethyl acetate/methanol/ammonium hydroxide) to provide N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanamide.

Example 14: (a) To a solution of 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-carboxytetrahydrothiopyran (413.0 mg, 1.0 mmol) in methylene chloride (10 mL) containing dimethylformamide (80.0 mg, 1.1 mmol) is added a 2N solution of oxalyl chloride in methylene chloride (1.0 ml, 2.0 mmol) at -10 °C. The mixture is allowed to warm to 20 °C for 30 minutes. This mixture is added to a pre-stirred mixture of hydroxylamine hydrochloride (280.0 mg, 4.0 mmol) in tetrahydrofuran (10 ml)/water (1 ml) containing triethylamine (650.0 mg, 6.0 mmol) at 0 °C dropwise. The reaction mixture is allowed to slowly warm to room temperature and stirring is continued for 1.5 days. The reaction is worked up by partitioning between 1 N hydrochloric acid and ethyl acetate. The aqueous layer is removed and repeatedly extracted with ethyl acetate. The combined organic layers are dried (Na_2SO_4) and the solvent is evaporated. The crude product is purified by silica gel chromatography (2% methanol/methylene chloride) to give 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-tetrahydrothiopyran, m.p. 179-181 °C.

The starting material is prepared as follows:

A solution of tetrahydrothiopyran-4-one (4.64 g, 40.0 mmol) in methanol (10 mL) is added to a mixture of sodium cyanide (2.0 g, 40.0 mmol) and ammonium chloride (2.36 g, 44.0 mmol) in water (8 mL). The reaction mixture is heated to reflux for 14 hours. The mixture is diluted with water, basified with potassium carbonate, and extracted with diethyl ether. The organic extract is dried ($MgSO_4$) and filtered. The solution is acidified with hydrochloric acid saturated with methylene chloride. The resulting precipitate is filtered off providing 4-amino-4-cyano-tetrahydrothiopyran hydrochloride salt.

A solution of 4-amino-4-cyano-tetrahydrothiopyran (5.4 g, 30.3 mmol) in 6N aqueous hydrochloric (250 mL) acid is heated to reflux for 24 hours. The mixture is triturated by addition of methanol/toluene, and filtered. To the crude product, 4-amino-4-carboxytetrahydrothiopyran is added 40 ml of methanol followed by careful addition of thionyl chloride (3.0 ml, 41.1 mmol). The reaction mixture is heated to reflux for 12 hours, cooled to room temperature, and concentrated in vacuo to a reduced volume. The remaining mixture is triturated with ethyl acetate/diethyl ether, and the product is collected by filtration, to give 4-amino-4-carbomethoxy-tetrahydrothiopyran hydrochloride.

To a solution of 4-amino-4-carbomethoxy-tetrahydrothiopyran hydrochloride (3.1 g, 15.0 mmol) in methylene chloride (75 mL) containing triethylamine (3.5 g, 330.0 mmol) is added 4-methoxybenzenesulfonyl chloride (4.1 g, 20.0 mmol) at room temperature. The reaction mixture is stirred at room temperature for 18 hours. The mixture is diluted with water and the organic layer is removed. The aqueous layer is extracted with diethyl ether and the organic extracts are washed with brine, dried ($MgSO_4$) and the solvent is evaporated. The product is purified by silica gel chromatography (50% ethylacetate/hexanes) to provide 4-[[4-methoxybenzenesulfonyl]amino]-4-carbomethoxy-tetrahydrothiopyran.

To a solution of 4-[[(4-methoxybenzene)sulfonyl]amino]-4-carbomethoxy-tetrahydrothiopyran (690.0 mg, 2.0 mmol) in dimethylformamide (20 mL) at 0 °C is added sodium hydride (100.0 mg, 2.5 mmol, 60% in oil) and benzyl bromide (0.5ml, 4.2 mmol). The reaction mixture is allowed to warm to room temperature and stirred for 16 hours. The mixture is quenched by addition of water and extracted with 50% ethyl acetate/diethyl ether. The combined organic extracts are dried ($MgSO_4$), filtered, and the solvent is evaporated. The product is purified by silica gel chromatography (50% diethyl ether/hexanes) to provide 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-carbomethoxy-tetrahydrothiopyran.

To a solution of 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-carbomethoxytetrahydrothiopyran (800.0 mg, 1.9 mmol) in methanol (50 mL) is added 1 N sodium hydroxide (25 mL). The mixture is heated to reflux for 10 hours, and then solid sodium hydroxide is added (3.0 g, excess) and refluxing is continued for 18 hours. The mixture is concentrated to a volume of approximately 30 mL and acidified with citric acid (pH = 5). The mixture is partitioned between ethyl acetate and water. The organic layer is removed, washed with brine, dried ($MgSO_4$), and the solvent is evaporated to give 4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-4-carboxytetrahydrothiopyran.

(b) Similarly prepared is 4-[N-hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-tetrahydropyran, m.p. 137-140 °C, by starting with tetrahydropyran-4-one in the first step, and carrying out the subsequent steps as described above.

(c) Similarly prepared is 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](benzyl)amino]-cyclohexane, m.p. 149-151 °C, by using commercially available 1-aminocyclohexanecarboxylic acid in the second step, and carrying out the subsequent steps as described above.

(d) Similarly prepared is 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](benzyl)amino]-cyclopentane, m.p. 67.0-68.0 °C, by using commercially available 1-aminocyclopentane carboxylic acid in the second step, and carrying out the subsequent steps as described above.

(e) Similarly prepared is 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-cyclohexane, m.p. 115 °C, by using 1-aminocyclohexanecarboxylic acid in the second step, alkylating 1-[carbomethoxy]-1-[[(4-methoxybenzene)sulfonyl]amino]-cyclohexane with 3-picolyl chloride in the third step, and carrying out the other steps as described above.

(f) Similarly prepared is 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](3-picolylamino]-cyclopropane hydrochloride, m.p. 205-207 °C, starting with 1-amino-1-cyclopropanecarboxylicacid.

Example 15: 4-[N-t-Butyloxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-piperidine is dissolved in dichloroethane (60 mL) and ethanol (1.0 mL) in a glass sealed tube. Hydrochloric acid gas (from a lecture bottle) is bubbled through the solution for 30 minutes at -10 °C. The tube is sealed, gradually warmed to room temperature, and stirred overnight. At this point, hydrochloric acid gas is again bubbled through the reaction mixture as done previously and stirred at room temperature for an additional 24 hours. The reaction mixture is reduced to 1/3 volume in vacuo and triturated with diethyl ether. The solid is filtered off and dried in vacuo to provide 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[benzyl]-piperidine, m.p. 135.5-142 °C.

The starting material is prepared as follows:

A mixture of N-carboethoxy-4-piperidone (88.6 g, 517.2 mmol), sodium cyanide (30.0 g, 612.1 mmol) in water (54 mL), ammonium chloride (34.0 g, 635.5 mmol) in water (72 mL), and ammonium hydroxide (76 ml) is heated to 60-65 °C for 5 hours, and then stirred at room temperature overnight. The resulting solid is filtered off, dissolved in methylene chloride, and washed with a small amount of brine. The organic layer is dried ($MgSO_4$), concentrated in vacuo to 1/2 volume, and triturated with hexane. The resulting precipate is collected by filtration and dried under vacuum, to give N-carboethoxy-4-amino-4-cyanopiperidine.

A solution of N-carboethoxy-4-amino-4-cyanopiperidine (82.0 g) in water (700 mL) containing concentrated hydrochloric acid (800 mL) is stirred at room temperature for 4 days. The solvent is then evaporated to give 4-amino-4-carboxypiperidine dihydrochloride.

Into a heterogeneous mixture of 4-amino-4-carboxypiperidine dihydrochloride (61.0 g, 0.34 mmol) in methanol (600 mL) is bubbled hydrogen chloride gas at room temperature. The reaction mixture is concentrated to dryness in vacuo, dissolved in 1,4-dioxane (200 mL), and concentrated in vacuo. The residue is redissolved in methanol (1600 mL) into which hydrogen chloride gas is bubbled for 45 minutes. The reaction mixture is refluxed for 18 hours. Most of the solvent is then evaporated, the product is collected by filtration, and washed with ethyl acetate to give 4-amino-4-carbomethoxypiperidine dihydrochloride.

To a mixture of 4-amino-4-carbomethoxypiperidine dihydrochloride (6.60 g, 28.7 mmol) and potassium carbonate (18.8 g, 143.5 mmol) in dioxane/water (350 ml/176 ml) at 0 °C is added di-t-butyl-dicarbonate (8.14 g, 37.31 mmol) in dioxane (60 mL) over 2 hours. The reaction mixture is warmed to room temperature and stirred for 8 hours. To this mixture is added a solution of 4- methoxybenzenesulfonyl chloride (7.71 g, 37.31 mmol) in dioxane (60 mL) at 0 °C. The reaction mixture is stirred at room temperature overnight. An additional portion of 4- methoxybenzenesulfonyl chloride (7.71 g, 37.31 mmol) in dioxane (60 mL) is added to the mixture at 0 °C. The reaction mixture is allowed to warm to room temperature and stirred overnight. The mixture is concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The aqueous layer is removed, saturated with sodium chloride, and re-extracted with ethyl acetate. The combined extracts are dried (MgSO4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (50% ethylacetate/hexane) to provide 4-[[4-methoxybenzenesulfonyl]amino]-1-[(t-butoxycar-

bonyl]-4-[carbomethoxy]-piperidine, contaminated with a small amount of 4-methoxybenzene-sulfonic acid.

To a solution of 4-[[4-methoxybenzenesulfonyl]amino]-1-[(t-butoxycarbonyl]-4-[carbomethoxy]-piperidine (4.0 g, 9.30 mmol) in dimethylformamide (150 mL) at 0 °C is added sodium hydride (1.12 g, 28.0 ml, 60% in oil) followed by benzyl bromide (4.8 g, 28.0 mmol). The reaction mixture is allowed to warm to room temperature for 1 hour. The mixture is quenched with water and extracted with diethyl ether. The organic extract is dried ($MgSO_4$) and the solvent is evaporated. The crude product is purified by silica gel chromatography (50% ethyl acetate/hexanes) to provide 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[(t-butoxycarbonyl]-4-[carbomethoxy] piperidine.

To a solution of 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[(t-butoxycarbo nyl]-4-(carbomethoxy]-piperidine (1.8 g, 3.47 mmol) in ethyl acetate (10 mL) is added a hydrogen chloride gas saturated methylene chloride solution (15 mL). The reaction mixture is stirred for 4 hours at room temperature. The mixture is concentrated in vacuo to give 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-[carbomethoxy]-piperidine.

To a solution of 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-[carbomethoxy]- - piperidine (1.0 g, 2.39 mmol) in dimethylformamide (160 mL) is added sodium hydride (287.0 mg, 7.18 mmol, 60% in oil) at 0 °C, followed by benzyl bromide (450.0 mg, 2.63 mmol). The reaction mixture is slowly warmed to room temperature and stirred overnight. The mixture is quenched with water and extracted with ethyl acetate. The combined organic layers are washed with brine, dried (Na_2SO_4) and the solvent is evaporated to give 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-4-[carbomethoxy]-piperidin e.

A heterogeneous mixture of 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-4-[carbomethoxy]-piperidine (1.2 g, 2.26 mmol) in 50% aqueous sodium hydroxide (10 mL) and methanol (50 mL) is heated to reflux for 16 hours. The methanol is evaporated and the residue is neutralized with 4 N hydrochloric acid. The aqueous solution is extracted with ethyl acetate. The combined organic extracts are dried ($NaSO_4$) and the solvent is evaporated to give 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-4-[carboxy]-piperidine.

To a mixture of 4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-4-[carboxy]-piperidine (850.0 mg, 1.64 mmol) in methylene chloride (100 mL) containing N-methylmorpholine (0.6 ml, 5.48 mmol) and O-t-butylhydroxyl amine hydrochloride (620.0 mg, 4.94 mmol) is added N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (1.1 g, 5.74 mmol). The reaction mixture is stirred overnight at room temperature. The mixture is diluted with water and extracted with methylene chloride. The combined organic extracts are dried (Na_2SO_4) and the solvent is evaporated. The crude product is purified by silica gel chromatography (ethyl acetate) to provide 4-[N-t-butyloxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[benzyl]-piperidine.

Alternately, 4-[[4-methoxybenzenesulfonyl]amino]-1-[(t-butoxycarbonyl]-4-carbomethoxy]-piperidine is first hydrolyzed with sodium hydroxide to 4-[[4-methoxybenzenesulfonyl]amino]-1-[(t-butoxycarbonyl]-4-[carboxy]-piperidine. Treatment with O-t-butylhydroxylamine under conditions described above gives 4-[N-t-butyloxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[t-butoxycarbonyl]-piperidine. Reaction with 1N hydrochloric acid in ethyl acetate yields 4-[N-t-butyloxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl]-(benzyl)amino]-piperidine, which is treated with benzyl bromide as described above.

Similarly prepared, starting from 4-[[4-methoxybenzenesulfonyl(benzyl)amino]-4-[carbomethoxy]-piperidine, are the following:

(a) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[dimethylaminoacetyl]-piperidine hydrochloride, m.p. 145 °C;

(b) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl(benzyl)-amino]-1-[3-picolyl]-piperidine dihydrochloride, m.p. 167 °C;

(c) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-(carbomethoxymethyl]-piperidine hydrochloride, m.p. 183.5-185 °C;

(d) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-piperidine trifluoroacetate;

(e) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[t-butoxycarbonyl]-piperidine;

(f) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[methylsulfonyl]-piperidine;

(g) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[methyl]piperidine hydrochloride, m.p. 185.5-187 °C;

(h) 4-[N-Hydroxycarbamoyl]-4-[[methoxybenzenesulfonyl](benzyl)amino]-1-[morpholinocarbonyl]-piperidine, m.p. 89-91 °C;

(i) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[4-picolyl]piperidine dihydrochloride, m.p. 168 °C.

Example 16: Ethyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]acetate (11.20 g, 30.9 mmol) is dissolved in methanol (100 mL). To this solution is added hydroxylamine hydrochloride (4.31 g, 62.0 mmol), followed by the addition of sodium methoxide, freshly prepared from sodium (2.14 g, 93.0 mmol) dissolved in methanol (55 mL). The reaction is stirred overnight at room temperature. The reaction is worked up by partitioning between dilute hydrochloric acid (pH = ~3) and ethyl acetate. The aqueous phase is extracted well with ethyl acetate, the combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (75 % ethyl acetate/ hexane) to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-acetamide, m.p. 112-114 °C.

The starting material is prepared as follows:

Benzylamine (16.0 mL, 145.2 mmol) is dissolved in chloroform (110 mL), and the solution is cooled to 0 °C. To this solution is added 4-methoxybenzenesulfonyl chloride (10.0 g, 48.4 mmol). The reaction is stirred at room temperature for 1 hour, and then refluxed for 1 hour. After cooling back to room temperature, the reaction is washed three times with 4N hydrochloric acid (200 mL), twice with water (100 mL), once with brine (50 mL), then dried (Na_2SO_4), and the solvent is evaporated to give N-[4-methoxybenzenesulfonyl]-benzylamine.

Sodium hydride (1.56 g of a 50 % oil dispersion, 33.0 mmol) is suspended in tetrahydrofuran (85 mL). To this is added a solution of N-[4-methoxybenzenesulfonyl]-benzylamine (9.0 g, 32.5 mmol) also in tetrahydrofuran (85 mL), and the reaction is stirred for 30 minutes at room temperature. Then ethyl bromoacetate (5.40 mL, 48.8 mmol) is added, and the reaction is stirred overnight at room temperature. The reaction is quenched with a small amount of water, and all the solvent is removed. The crude mixture is partitioned between ethyl acetate and water, the aqueous phase is extracted several times with ethyl acetate, the combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (30% ethyl acetate/hexane) to give ethyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]acetate.

Example 17: The following compounds are prepared similarly to Example 16:

(a) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 133-134 °C, by coupling isobutylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(b) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclohexylmethyl)amino]acetamide, m.p. 145-146 °C, by coupling cyclohexanemethylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(c) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclohexyl)amino]acetamide, m.p. 148-149 °C, by coupling cyclohexylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(d) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](phenethyl)amino]acetamide, m.p. 137-138 °C, by coupling phenethylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(e) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-methylbutyl)amino]acetamide, m.p. 108 °C, by coupling 1-amino-3-methylbutane with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(f) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](sec-butyl)amino]acetamide, m.p. 138 °C, by coupling (sec)-butylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(g) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](tert-butyl)amino]acetamide, m.p. 150-151 °C, by coupling (tert)-butylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(h) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]acetamide, m.p. 115-119 °C, by coupling 4-fluorobenzylamine with 4–methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(i) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-chlorobenzyl)amino]acetamide, m.p. 121-123 °C, by coupling 4-chlorobenzylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16. (j) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isopropyl)-amino]acetamide, m.p.
139-141 °C, by coupling isopropylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(k) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-methylbenzyl)amino] acetamide, m.p. 133-135 °C, by coupling 4-methylbenzylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(l) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-phenyl-1-propyl)amino]acetamide by coupling 3-phenyl-1-propylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(m) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbutyl)amino]acetamide, m.p. 109-112 °C, by coupling 4-phenylbutylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(n) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-cyclohexylethyl)amino]acetamide, m.p. 143-144 °C, by coupling 2-cyclohexylethylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(o) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbenzyl)amino]acetamide by coupling 4-phenylbenzylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(p) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2,2,2-trifluoroethyl)amino]acetamide, m.p. 142-143 °C, by coupling 2,2,2-trifluoroethylamine with 4-methoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(q) N-Hydroxy-2-[[benzenesulfonyl](isobutyl)amino]acetamide, m.p. 130-131 °C, by coupling isobutylamine with benzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(r) N-Hydroxy-2-[[4-trifluoromethylbenzenesulfonyl](isobutyl)amino]acetamide, m.p. 130-131 °C, by coupling isobutylamine with 4-trifluoromethylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(s) N-Hydroxy-2-[[4-chlorobenzenesulfonyl](isobutyl)amino]acetamide, m.p. 126-127 °C, by coupling isobutylamine with 4-chlorobenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(t) N-Hydroxy-2-[[4-methylbenzenesulfonyl](isobutyl)amino]acetamide, m.p. 138-140 °C, by coupling isobutylamine with 4-methylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(u) N-Hydroxy-2-[[4-fluorobenzenesulfonyl](isobutyl)amino]acetamide, m.p. 144-146 °C, by coupling isobutylamine with 4-fluorobenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(v) N-Hydroxy-2-[[2-thiophenesulfonyl](isobutyl)amino]acetamide by coupling isobutylamine with 2-thiophenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(w) N-Hydroxy-2-[[benzenesulfonyl](benzyl)amino]acetamide, m.p. 90-93 °C, by coupling benzylamine with benzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(x) N-Hydroxy-2-[[4-nitrobenzenesulfonyl](isobutyl)amino]acetamide, m.p. 128-130 °C, by coupling isobutylamine with 4-nitrobenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(y) N-Hydroxy-2-[[4-(tert)-butylbenzenesulfonyl](isobutyl)amino]acetamide, m.p. 113-114 °C, by coupling isobutylamine with 4-(tert)-butylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(z) N-Hydroxy-2-[[4-methylsulfonylbenzenesulfonyl](isobutyl)amino]acetamide, m.p. 159-161 °C, by coupling isobutylamine with 4-methylsulfonylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(aa) N-Hydroxy-2-[[3-trifluoromethylbenzenesulfonyl](isobutyl)amino]acetamide m.p. 140-141 °C, by coupling isobutylamine with 3-trifluoromethylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(bb) N-Hydroxy-2-[[2,4,6-trimethylbenzenesulfonyl](isobutyl)amino]acetamide, m.p. 142-143 °C, by coupling isobutylamine with 2,4,6-trimethylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(cc) N-Hydroxy-2-[[2,5-dimethoxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 50-53 °C, by coupling isobutylamine with 2,5-dimethoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(dd) N-Hydroxy-2-[[3,4-dimethoxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 146-148 °C, by coupling isobutylamine with 3,4-dimethoxybenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(ee) N-Hydroxy-2-[[2,4,6-triisopropylbenzenesulfonyl](isobutyl)amino]acetamide, m.p. 131-133 °C, by coupling isobutylamine with 2,4,6-triisopropylbenzenesulfonyl chloride in the first step, and carrying out the subsequent steps as described above.

(ff) N-Hydroxy-2-[[3,5-dimethylisoxazole-4-sulfonyl(benzyl)amino]acetamide, m.p. 140 °C, by coupling benzylamine with 3,5-dimethylisoxazole-4-sulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

(gg) N-Hydroxy-2-[[2,4-dimethylthiazole-5-sulfonyl(benzyl)amino]acetamide, m.p. 55 °C, by coupling benzylamine with 2,4-dimethylthiazole-5-sulfonyl chloride in the first step, and carrying out the subsequent steps as described in example 16.

Example 18: Ethyl 2-[[4-methoxybenzenesulfonyl](4-methoxybenzyl)amino]acetate (0.90 g, 2.3 mmol) is dissolved in methanol (20 mL). To this solution is added hydroxylamine hydrochloride (0.80 g, 11.5 mmol), followed by the addition of sodium methoxide (5.2 mL of a 2.67M solution). The reaction is stirred overnight at room temperature. The reaction is worked up by partitioning between dilute hydrochloric acid (pH = ~3) and ethyl acetate. The aqueous phase is extracted well with ethyl acetate, the combined organic layers are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The product is recrystallized from ether/ethyl acetate to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](4-methoxybenzyl)amino]acetamide, m.p. 134-135.5 °C.

The starting material is prepared as follows:

Glycine ethyl ester hydrochloride (31.39 g, 225.0 mmol) is dissolved in dioxane (150 mL) and water (150 mL), triethylamine (69.0 mL, 495.0 mmol) is added, and the solution is cooled to 0 °C. To this solution is added 4-methoxybenzenesulfonyl chloride (51.15 g, 248.0 mmol) over 10 minutes. The reaction is warmed to room temperature and stirred overnight. The next day the mixture is reduced to one-half volume by evaporating solvent, diluted with 1N sodium hydroxide, and extracted well with ether. The combined organic layers are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The product is recrystallized from ether/ethyl acetate/hexanes to give ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate.

To a suspension of sodium hydride (0.906 g, 22.67 mmol) in dimethylformamide (50.0 mL), is added ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate (4.13 g, 15.11 mmol) and 4-methoxybenzyl chloride (2.17 mL, 15.87 mmol), and the reaction is stirred overnight at room temperature. The reaction is cooled to 0 °C, quenched with 1N hydrochloric acid, and extracted well with ether. The combined organic layers are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The product is recrystallized from ether/hexanes to give ethyl 2-[[4-methoxybenzenesulfonyl](4-methoxybenzyl)amino]acetate.

Example 19: The following compounds are prepared similarly to example 18:

(a) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]acetamide, m.p. 138.5-139.5 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with 2-picolyl chloride in the second step, and carrying out the other steps as described in example 18.

(b) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]acetamide, m.p. 144-145 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with 3-picolyl chloride in the second step, and carrying out the other steps as described in example 18.

(c) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](piperonyl)amino]acetamide, m.p. 143-144 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with piperonyl chloride in the second step, and carrying out the other steps as described in example 18.

(d) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-piperidinylethyl)amino]acetamide, m.p. 120-122 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with N-(2-chloroethyl)-piperidine in the second step, and carrying out the other steps as described in example 18.

Example 20: (a) N-(t-Butyloxy)-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetamide (1.15g, 2.42 mmol) is dissolved in methylene chloride (30.0 mL) and ethanol (0.20 mL) in a glass sealed tube. Hydrochloric acid gas (from a lecture bottle) is bubbled through the solution for 20 minutes, and then the tube is sealed and stands at room temperature overnight. The next day, additional hydrochloric acid gas is bubbled through the solution for 20 minutes, more ethanol (0.20 mL) is added, and then the tube is sealed and stands at room temperature for two days. After that time, the solvent is removed. The product is purified by silca gel chromatography (5% to 15% methanol/methylene chloride with ~1% ammonium hydroxide) to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetamide, m.p. 177-178 °C.

The starting material is prepared as follows:

To a suspension of sodium hydride (0.84 g, 35.0 mmol) in dimethylformamide (120.0 mL), is added ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate (3.19 g, 11.67 mmol) and 2-(chloromethyl)quinoline (2.62 g, 12.26 mmol), and the reaction is stirred for three days at room temperature. Then, additional NaH (0.46 g, 11.67 mmol) is added, and the reaction is heated to 50 °C for 5 hours. The reaction is cooled to 0 °C,

quenched with water, and extracted well with ether. The combined organic layers are washed with brine, dried (Na_2SO_4), and the solvent is removed to give ethyl 2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetate.

Ethyl 2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetate (4.0g, 9.63 mmol) is dissolved in tetrahydrofuran (70.0 mL). To this solution is added lithium hydroxide (18.0 mL of a 1N aqueous solution, 18.0 mmol), and the reaction is stirred at room temperature overnight. The tetrahydrofuran is evaporated, the reaction is then acidified to pH = ~3 using 1N hydrochloric acid, and extracted well with ethyl acetate.

The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated to give 2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetic acid hydrochloride.

2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetic acid hydrochloride (1.49 g, 3.35 mmol), 1-hydroxybenzotriazole (0.539 g, 3.52 mmol), 4-methylmorpholine (1.55 mL, 14.9 mmol), and O-t-butylhydroxyl amine hydrochloride (0.464 g, 3.70 mmol) are dissolved in methylene chloride (50.0 mL), and the reaction is cooled to 0 °C. To this solution is added N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (1.35 g, 7.04 mmol), and the reaction is allowed to warm up to room temperature and stir overnight. The reaction is diluted with more methylene chloride, and the organic layer is washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent is evaporated. The product is purified by silica gel chromatography (1% methanol/methylene chloride) to give N-(t-butyloxy)-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetamide.

(b) Similarly prepared is N-hydroxy-2-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-acetamide hydrochloride, m.p. 193 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with 4-picolyl chloride in the second step, and carrying out the other steps as described above.

Example 21: (a) 2-[[4-Methoxybenzenesulfonyl](6-chloropiperonyl)amino]acetic acid (1.87 g, 4.51 mmol) is dissolved in methylene chloride (45.0 mL). To this solution is added oxalyl chloride (0.784 mL, 9.02 mmol) and dimethylformamide (0.35 mL, 4.51 mmol), and the reaction is stirred at room temperature for 60 minutes. Meanwhile, in a separate flask, hydroxylamine hydrochloride (1.25 g, 18.04 mmol) and triethylamine (3.77 mL, 27.06 mmol) are stirred in tetrahydrofuran (20.0 mL) and water (5.0 mL) at 0 °C for 15 minutes. After 60 minutes, the methylene chloride solution is added in one portion to the second flask, and the combined contents are stirred overnight as the flask gradually warms up to room temperature. The reaction is then diluted with acidic water (pH = ~3), and extracted several times with ethyl acetate. The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is recrystallized from ethyl acetate/methanol/acetone to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)-amino] acetamide, m.p. 168-169 °C.

The starting material is prepared as follows:

To a suspension of sodium hydride (1.08 g, 27.06 mmol) in dimethylformamide (180.0 mL), is added ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate (4.93 g, 18.04 mmol) and 6-chloropiperonyl chloride (3.88 g, 19.0 mmol), and the reaction is stirred overnight at room temperature. The reaction is cooled to 0 °C, quenched with 1N hydrochloric acid, and extracted well with ether. The combined organic layers are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The product is recrystallized from ether/hexanes to give ethyl 2-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino]acetate.

Ethyl 2-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino]acetate (2.12g, 4.79 mmol) is dissolved in tetrahydrofuran (40.0 mL). To this solution is added lithium hydroxide (10.0 mL of a 1N aqueous solution, 10.0 mmol), and the reaction is stirred at room temperature overnight. The tetrahydrofuran is evaporated, the reaction is then acidified to pH = ~3 using 1N hydrochloric acid, and extracted well with ethyl acetate. The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated to give 2-[[4-methoxybenzenesulfonyl](6- chloropiperonyl)amino]acetic acid.

(b) Similarly prepared is N-hydroxy-2-[[4-methoxybenzenesulfonyl](3,4,5-trimethoxybenzyl)amino]-acetamide, m.p. 116-118 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with 3,4,5-trimethoxybenzyl chloride in the second step, and carrying out the other steps as described above.

(c) Similarly prepared is N-hydroxy-2-[[4-methoxybenzenesulfonyl](3-methoxybenzyl)amino]acetamide, m.p. 118-119 °C, by alkylating ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate with 3-methoxybenzyl chloride in the second step, and carrying out the other steps as described above.

Example 22: Ethyl 2-[[4-methoxybenzenesulfonyl](2-[4-morpholino]ethyl)amino]acetate (7.1 g, 18.4 mmol) is dissolved in ethanol (100 mL), followed by the addition of sodium spheres (1.1 g). To this solution is added hydroxylamine hydrochloride (2.47 g, 35.5 mmol). The reaction is refluxed overnight. The reaction is worked up by removing most of the solvent, and partitioning between saturated sodium bicarbonate and ethyl acetate. The aqueous phase is extracted well with ethyl acetate, the combined organic layers are washed with brine, dried ($MgSO_4$), and the solvent is evaporated. The product is purified by silica gel chromatography (80% ethyl acetate/16% methanol/4% acetic acid). The solvent is removed to give the

product containing residual acetic acid. The product is partitioned between ethyl acetate and water (pH = 7.1), the organic phase is dried ($MgSO_4$), and the solvent is concentrated and then triturated with ether to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-[4-morpholino]ethyl)amino]acetamide, m.p. 108-112 °C.

The starting material is prepared as follows:

Ethyl 2-[[4-methoxybenzenesulfonyl]amino]acetate (13.7 g, 50.0 mmol) is dissolved in ethanol (500 mL), followed by the addition of sodium spheres (2.5 g, 109.0 mmol). To this solution is added N-(2-chloroethyl)-morpholine hydrochloride (10.0 g, 53.7 mmol), the reaction is stirred at room temperature for 2 hours, and then refluxed for 1.5 hours. The reaction is partitioned between ethyl acetate and brine. The aqueous phase is extracted well with ethyl acetate, the combined organic layers are dried ($MgSO_4$), and the solvent is evaporated to give ethyl 2-[[4-methoxybenzenesulfonyl](2-[4-morpholino]ethyl)amino]acetate.

Example 23: N-Hydroxy-2-[[4-aminobenzenesulfonyl](isobutyl)amino]acetamide, m.p. 50-55 °C, is obtained by hydrogenation of N-hydroxy-2-[[4-nitrobenzenesulfonyl](isobutyl)amino]acetamide (see example 17x), m.p. 128-130 °, using 10% palladium on carbon.

The starting material is prepared according to example 16 by coupling isobutylamine and 4-nitrobenzenesulfonyl chloride in the first step thereof.

Example 24: N-Hydroxy-2-[[4-dimethylaminobenzenesulfonyl](isobutyl)amino]acetamide, m.p. 127-129 °C, is obtained by methylation of N-hydroxy-2-[[4-aminobenzenesulfonyl](isobutyl)amino]acetamide using the procedure from Synthesis p. 709, 1987.

Example 25: Ethyl 2-[[4-hexyloxybenzenesulfonyl](isobutyl)amino]acetate (1.22 g, 3.05 mmol) is dissolved in methanol (15 mL). To this solution is added hydroxylamine hydrochloride (0.43 g, 6.11 mmol), followed by the addition of sodium methoxide, freshly prepared from sodium (0.35 g, 15.3 mmol) dissolved in methanol (5 mL). The reaction is stirred for 36 hours at room temperature. The reaction is worked up by partitioning between dilute hydrochloric acid (pH = ~3) and ethyl acetate. The aqueous phase is extracted well with ethyl acetate, the combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is crystallized from hexnae/ethyl acetate and collected by filtration to give N-hydroxy-2-[[4-hexyloxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 108-110 °C.

The starting material is prepared as follows:

A solution of ethanethiol (15 mL) and methylene chloride (15 mL) is cooled to 0 °C. Aluminum trichloride (9.62 g, 72.2 mmol) is added (the solution turns green), and the reaction is warmed to room temperature. Ethyl 2-[[4-methoxybenzenesulfonyl](isobutyl)amino]acetate (4.75 g, 14.44 mmol) is added in methylene chloride (5 mL), and the reactiom is stirred for 3.5 hours at room temperature. The reaction is then slowly quenched with water, and the crude reaction is partitioned between water and methylene chloride. The aqueous layer is extracted well with methylene chloride, the combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (25% to 50% ethyl acetate/hexane) to give ethyl 2-[[4-hydroxybenzenesulfonyl](isobutyl)amino]acetate.

Ethyl 2-[[4-hydroxybenzenesulfonyl](isobutyl)amino]acetate (1.0 g, 3.17 mmol) is dissolved in dimethylformamide (16 mL). Cesium carbonate (1.03 g, 3.17 mmol) is added, followed by 1-iodohexane (0.47 mL, 3.17 mmol), and the reaction is stirred overnight at room temperature. The reaction is then partitioned between water and ethyl acetate, the aqueous layer is extracted well with ethyl acetate, the combined organic layers are dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (10% ethyl acetate/hexane) to give ethyl 2-[[4-hexyloxybenzenesulfonyl](isobutyl)amino]-acetate.

Example 26: The following compounds are prepared similarly to example 25:

(a) N-Hydroxy-2-[[4-ethoxybenzenesulfonyl](isobutyl)amino]acetamide,by using ethyl iodide in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

(b) N-Hydroxy-2-[[4-butyloxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 125-127 °C, by using iodobutane in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

(c) N-Hydroxy-2-[[4-(3-methyl)butyloxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 93-96 °C, by using 1-iodo-3-methylbutane in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

(d) N-Hydroxy-2-[[4-heptyloxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 120-123 °C, by using 1-iodoheptane in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

(e) N-Hydroxy-2-[[4-(cyclohexylmethoxy)benzenesulfonyl](isobutyl)amino]acetamide, m.p. 75-80 °C, by using cyclohexylmethyl bromide in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

(f) N-Hydroxy-2-[[4-isopropyloxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 65-66 °C, by using isopropyl bromide in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

(g) N-Hydroxy-2-[[4-ethoxyethoxybenzenesulfonyl](isobutyl)amino]acetamide, m.p. 111-114 °C, by using 2-bromoethyl ethyl ether in the cesium carbonate alkylation step, and carrying out the subsequent steps as described in example 25.

Example 27: (a) N-(t-butyloxy)-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)-methyl]acetamide (0.77 g, 1.55 mmol) is dissolved in methylene chloride (2.0 mL) and ethanol (0.1 mL) in a glass sealed tube, and the reaction is cooled to 0 °C. Hydrochloric acid gas (from a lecture bottle) is bubbled through the solution for 20 minutes, and then the tube is sealed at room temperature for 3 days. After that time, the solvent is removed, and the reaction is partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (2% methanol/methylene chloride) to give N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetamide, m.p. 72-75 °C.

The starting material is prepared as follows:

D-asparagine (13.2 g, 100.0 mmol) is dissolved in dioxane (75.0 mL) and water (125.0 mL), triethylamine (21.0 mL, 150.0 mmol) is added, and the solution is cooled to 0 °C. To this solution is added 4-methoxybenzenesulfonyl chloride (22.7 g, 110.0 mmol) over 10 minutes. The reaction is warmed to room temperature and stirred for 3 days. The precipitate is then filtered off, the filtrate is acidified to pH = ~4, and extracted well with ethyl acetate. A first crop of pure product precipitates from the ethyl acetate and is collected by filtration. A second crop is obtained by evaporating off the ethyl acetate, and rinsing the solid obtained with water to remove inorganic salts. The two crops are combined to give N-[4-methoxybenzenesulfonyl]-(D)-asparagine.

N-[4-methoxybenzenesulfonyl]-(D)-asparagine (10.1 g, 33.3 mmol) is dissolved in dimethylformamide (167.0 mL). Cesium carbonate (5.43 g, 16.66 mmol) is added, followed by the addition of methyl iodide (2.22 mL, 33.3 mmol), and the reaction is stirred overnight. The reaction is then diluted with saturated ammonium chloride (366.0 mL), and extracted well with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is recrystallized from toluene to provide N-[4-methoxybenzenesulfonyl]-(D)-asparagine methyl ester.

To a suspension of N-[4-methoxybenzenesulfonyl]-(D)-asparagine methyl ester (8.54 g, 27.0 mmol) in methylene chloride (47.0 mL) is added pyridine (10.9 mL, 135.0 mmol). Para-toluenesulfonyl chloride (10.3 g, 54.0 mmol) is added, and the reaction mixture is allowed to stand without stirring at room temperature overnight. The next day, saturated sodium bicarbonate is added (125.0 mL), and the mixture is stirred for 1 hour. The mixture is then diluted with water and extracted well with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is recrystallized from 20% tetrahydrofuran/methanol to provide methyl 2(R)-[[4-methoxybenzenesulfonyl]-amino]-4-cyano-propionate.

To a suspension of sodium hydride (0.93 g, 23.2 mmol) in dimethylformamide (95.0 mL), is added methyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-4-cyano-propionate (6.92 g, 23.2 mmol) in dimethylformamide (10.0 mL). After stirring at room temperature for 20 minutes, benzyl bromide (3.1 mL, 25.5 mmol) is added, and the reaction is stirred overnight at room temperature. The reaction is then partitioned between ethyl acetate and acidic water (pH = ~5), the organic layer is dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (40% ethyl acetate/hexane) to give methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-cyano-propionate.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-cyano-propionate (1.34 g, 3.47 mmol) in dimethylformamide (5.4 mL) is added triethylamine hydrochloride (0.95 g. 6.93 mmol) and sodium azide (0.45 g, 6.93 mmol). The reaction is stirred at 110 °C overnight. The next day, the solvent is evaporated, the residue is acidified with 1N hydrochloric acid (16.0 mL), and extracted well with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated to yield methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(5-tetrazolyl)methyl]acetate.

This crude tetrazole is dissolved in dimethylformamide (17.4 mL). Cesium carbonate (0.56 g, 1.73 mmol) is added, followed by the addition of methyl iodide (0.23 mL, 3.47 mmol), and the reaction is stirred overnight. The reaction is then diluted with brine and extracted well with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The product is purified by silica gel chromatography (40% ethyl acetate/hexane) to give separately the two regioisomers: methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-methyl-5-tetrazolyl)methyl]acetate (0.50 g); and methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetate.

Methyl 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5 -tetrazolyl)methyl]acetate (1.0 g, 2.27 mmol) is dissolved in tetrahydrofuran (11.3 mL) and water (11.3 mL). To this solution is added lithium hydroxide hydrate (0.095 g, 2.27 mmol), and the reaction is stirred at room temperature for 2 hours. The reaction is then acidified to pH = ~3 using 1N hydrochloric acid, and extracted well with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated to provide 2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetic acid (0.96 g).

2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetic acid (0.96 g, 2.24 mmol), 1-hydroxybenzotriazole (0.30 g, 2.24 mmol), 4-methylmorpholine (0.86 mL, 7.89 mmol), and O-t-butylhydroxylamine hydrochloride (0.30 g, 2.24 mmol) are dissolved in methylene chloride (75.0 mL). N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (0.86 g, 4.48 mmol) is added, and the reaction is stirred overnight. The reaction is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (50% ethyl acetate/hexane) to give N-(t-butyloxy)-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetamide.

(b) Similarly prepared is the other tetrazole regioisomer, N-hydroxy-2-[[4-methoxybenzenesulfonyl]-(benzyl)amino]-2-[(1-methyl-5-tetrazolyl)methyl]acetamide, m.p. 92-96 °C, by completing the synthesis as described above.

(c) Similarly prepared is N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(5-tetrazolyl)methyl]-acetamide, m.p. 91-94 °C, by completing the synthesis as described above, except trityl chloride is used to protect the tetrazole ring in place of methyl iodide.

(d) Similarly prepared is N-hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbenzyl)amino]-2-[(5-tetrazolyl)methyl]acetamide, m.p. 184 °C, by completing the synthesis as described above, except 4-chloromethylbiphenyl is used in place of benzyl bromide in the alkylation step.

Example 28: Oxalyl chloride (106 mL, 1.22 mol) is added over 1 hour to dimethylformamide (92 mL) in methylene chloride (1250 mL) at 0 °C. To this is added a solution of 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride (248 g, 0.6 mol) in dimethylformamide (450 mL) over 1 hour, maintaining the temperature at 0 °C. This solution is stirred an additional 2 hours at room temperature, and then added dropwise to a mixture of hydroxylamine (460 g of a 50% aqueous solution, 6.82 mol) in tetrahydrofuran (2400 mL). The reaction is stirred an additional 3 hours at 5 °C, and then at room temperature overnight. The reaction mixture is filtered, the organic layer is collected, and the solvent is evaporated. The crude product is re-dissolved in methylene chloride (2 L), washed with water (2 X 1 L), saturated sodium bicarbonate (4 X 1 L), brine (1 L), dried (Na_2SO_4), and the solvent is evaporated. The product is dissolved in ethyl acetate (700 mL) and diluted with ether (1400 mL) to induce precipitation. The pure product is collected by filtration to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide. After conversion to the hydrochloride salt, a white solid is obtained, m.p. 169-170 °C (dec).

The starting material is prepared as follows:

To a solution of D-valine (2000 g, 17.09 mol) in water (16.9 L) and acetone (9.5 L), cooled to 5 °C, is added triethylamine (4769 mL, 34.22 mol), and the reaction is stirred for 30 minutes. Then a solution of 4-methoxybenzenesulfonyl chloride (3524 g, 18.48 mol) in acetone (7.4 L) is added over 30 minutes, and the reaction is stirred at room temperature overnight. Most of the acetone is evaporated off, and the pH is adjusted to pH = 8.25 with 6N sodium hydroxide. The crude product is washed with toluene (2 X 10 L), and then the pH is re-adjusted to pH = 2.2 with 6N hydrochloric acid. The mixture is then extracted with methylene chloride (3 X 12 L), the combined organic layers are washed with 2N hydrochloric acid, water, dried (Na_2SO_4), and the solvent is evaporated to provide N-[4-methoxybenzenesulfonyl]-(D)-valine.

To a solution of N-[4-methoxybenzenesulfonyl]-(D)-valine (8369 g, 29.13 mol) in methanol (30 L) at 5 °C is added thionyl chloride (2176 mL, 29.7 mol) over 2.5 hours. After stirring for 3 hours at 5 °C, the reaction is stirred for 36 hours at room temperature. Most of the solvent is evaporated, and the crude product is dissolved in toluene (80 L). The toluene layer is then washed with water (20 L), saturated sodium bicarbonate (20 L), water again (20 L), 2N hydrochloric acid (20 L), brine (20 L), dried (Na_2SO_4), and the solvent is evaporated. The solid obtained is dissolved in ethyl acetate (8 L) and heptane (16 L) is added to induce crystallization. The precipitated product is collected by filtration to provide methyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-3-methylbutanoate.

To a solution of methyl 2(R)-[[4-methoxybenzenesulfonyl]amino]-3-methylbutanoate (1662 g, 5.52 mol) in dimethylformamide (10.9 L) is added 3-picolyl chloride hydrochloride (947.3 g, 5.77 mol) followed by powdered potassium carbonate (2409.9 g, 17.36 mol). The reaction mixture is stirred at room temperature for 2 days. At that time, additional quantities of 3-picolyl chloride hydrochloride (95 g) and powdered potassium carbonate (241 g) are added, and the reaction is stirred for 3 more days. The solids are then

filtered away, the crude product is poured into water (22 L), and the pH is adjusted to pH = 8 with 6N sodium hydroxide. This solution is extracted well with toluene (4 X 10 L), the combined organic layers are washed with water (2 X 12 L), and then with 6N hydrochloric acid (3 X 1600 mL). This aqueous layer is then re-adjusted to pH = 8 with 6N sodium hydroxide, extracted with toluene (4 X 10 L), dried (Na_2SO_4), and the solvent is evaporated. The oil obtained is re-dissolved in ethyl acetate (12 L), cooled to 5 °C, and to this is added methanolic HCl (834 mL). After stirring for 2 hours, the precipitated product is collected by filtration to give methyl 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoate hydrochloride.

Methyl 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoate hydrochloride (7164 g, 16.7 mol) is added to a solution of water (27 L) and concentrated hydrochloric acid (9 L), and heated to 120 °C for 3 days. After cooling down to room temperature, charcoal (350 g) is added, stirring is continued for 45 minutes, the reaction is filtered, and the solvent is evaporated. The crude solid is re-dissolved in methanol (7.1 L) and ethyl acetate (73 L), and cooled to 3 °C for 2 hours. The precipitated product is collected by filtration to give 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride.

Example 29: N-Benzyloxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide (see example 29a) is reacted with hydrogen in the presence of 10% palladium on charcoal catalyst at room temperature and atmospheric pressure to yield N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide. After conversion to the hydrochloride salt, a white solid is obtained, m.p. 169-170 °C (dec).

(a) The N-(benzyloxy) substituted prodrug derivative of the above compound is prepared as follows:
2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride is reacted with O-benzylhydroxylamine hydrochloride under conditions described for reaction with O-t-butylhydroxylamine hydrochloride to yield N-(benzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide, m.p. 74.5-76 °C.

(b) The corresponding N-(4-methoxybenzyloxy) substituted prodrug derivative, N-(4-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide, is prepared as follows:
2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride (2.41 g, 5.82 mmol), 1-hydroxybenzotriazole (0.786 g, 5.82 mmol), 4-methyl-morpholine (1.9 mL, 17.46 mmol), and O-(4-methoxybenzyl)hydroxylamine (1.78 g, 11.63 mmol) (prepared according to Pol. J. Chem. 55, 1163-1167 (1981)) are dissolved in methylene chloride (55 mL). N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (1.45 g, 7.57 mmol) is added, and the reaction is stirred overnight. The reaction is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (ethyl acetate followed by 5% methanol/ethyl acetate) to give N-(4-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide, m.p. 45-53 °C.

Similarly prepared are: (c) the N-(2,4-dimethoxybenzyloxy)-substituted prodrug derivative, N-(2,4-dimethoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide, m.p. 45-60 °C;

(d) the N-(2-methoxybenzyloxy)-substituted prodrug derivative, N-(2-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide m.p. 46-56 °C.

Example 30: N-(t-Butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3(R)-(3-picolyloxy)-butanamide (1.3 g, 2.4 mmol) is dissolved in methylene chloride (50 mL) containing ethanol (0.14 mL, 2.4 mmol) in a round bottom flask, and the reaction is cooled to -10 °C. Hydrochloric acid gas (from a lecture bottle) is bubbled through for 20 minutes. The reaction is sealed, allowed to slowly warm to room temperature, and stirred for two days. The solvent is reduced to 1/3 the volume by evaporation and the residue is triturated with ether. The mixture is filtered, the fiter cake is removed and dried in vacuo to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3(R)-(3-picolyloxy)-butanamide dihydrochloride as a white solid; $[\alpha]_D^{25} = +35.26°$ (c = 5.58, DMSO).

The starting material is prepared as follows:
To a solution of D-threonine (5.0 g, 0.042 mol) in water (50 mL) and dioxane (50 mL) containing triethylamine(8.9 mL, 0.063 mol) at room temperature is added 4-methoxybenzenesulfonyl chloride (9.54 g, 0.046 mol). The reaction mixture is stirred overnight at room temperature. Most of the dioxane is evaporated off, and the pH is adjusted to pH = 2 with 1N HCl. The mixture is then extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and concentrated in vacuo to provide N-[4-methoxybenzenesulfonyl]-(D)-threonine.

N-[4-methoxybenzenesulfonyl]-(D)-threonine (4.0 g, 13.84 mmol), 1-hydroxybenzotriazole (1.87 g, 13.84 mmol), 4-methylmorpholine (7.9 mL, 69.2 mmol), and O-t-butylhydroxylamine hydrochloride (5.22 g, 41.52 mmol) are dissolved in methylene chloride (100 mL). To this solution is added N-[dimethylaminopropyl]-N'-

ethylcarbodiimide hydrochloride (3.45 g, 17.99 mmol), and the reaction is stirred overnight. The mixture is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product is purified by silica gel chromatography (ethyl acetate) to give N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl]-amino]-3(R)-hydroxybutanamide.

To a solution of N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl]amino]-3(R)-hydroxybutanamide (3.04 g, 8.44 mmol) in dimethylformamide (150 mL) is added 3-picolyl chloride hydrochloride (1.45 g, 8.87 mmol) followed by potassium carbonate (11.65 g, 84.4 mmol). The reaction mixture is stirred at room temperature overnight, then heated to 45 °C for 5 hours. An additional amount of 3-picolyl chloride hydrochloride (692.0 mg, 4.23 mmol) is added at this point. The reaction mixture is stirred at 45 °C for 10 hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product is purified by silica gel chromatography (ethyl acetate, then 5% methanol/methylene chloride) to give N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3(R)-(3-picolyloxy)butanamide.

Example 31: (a) N-(t-Butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]cyclohexylacetamide (1.9 g, 3.9 mmol) is dissolved in dichloroethane (50 mL) containing ethanol (0.21 ml, 3.9 mmol) in a round bottom flask, and the reaction is cooled to -10 °C. Hydrochloric acid gas (from a lecture bottle) is bubbled through for 30 minutes. The reaction is sealed, allowed to slowly warm to room temperature, and stirred for 4 days. The solvent is reduced to 1/3 volume by evaporation and triturated with ether. The mixture is filtered, filter cake removed, and dried in vacuo to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-2-cyclohexylacetamide hydrochloride as a white solid, m.p. 154.5-156 °C.

The starting material is prepared as follows:

To a solution of D-cyclohexylglycine hydrochloride (10.4 g, 53.7 mmol) in 1:1 dioxane/water (200 mL) containing triethylamine (37.0 g, 366.0 mmol) at room temperature is added 4-methoxybenzenesulfonyl chloride (15.0 g, 73.0 mmol), and the reaction mixture is stirred at room temperature overnight. The mixture is then diluted with methylene chloride, washed with 1N aqueous hydrochloric acid and water. The organic layer is washed again with brine, dried (Na_2SO_4), and the solvent is evaporated to provide N-[4-methoxybenzenesulfonyl]-(D)-cyclohexylglycine as a crude product. A solution of this crude product in toluene (200 mL) containing N,N-dimethylformamide di-t-butyl acetal (48.5 mL, 200.0 mmol) is heated to 95 °C for 3 hours. The solvent is then evaporated. The crude product is purified by silica gel chromatography (30% ethyl acetate/hexanes) to provide N-[4-methoxybenzenesulfonyl](D)-cyclohexylglycine t-butyl ester.

To a solution of N-[4-methoxybenzenesulfonyl]-(D)-cyclohexylglycine t-butyl ester (2.0 g, 4.1 mmol) in dimethylformamide (100 mL) is added 4-picolyl chloride hydrochloride (0.74 g, 4.5 mmol) followed by potassium carbonate (5.61 g, 40.7 mmol). The reaction mixture is stirred at room temperature for 4 days. The mixture is then diluted with water and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (ethyl acetate) to give t-butyl 2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-2-cyclohexylacetate.

t-Butyl 2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-cyclohexyla cetate (2.0 g, 4.2 mmol) is dissolved in methylene chloride (80 mL) and cooled to -10 °C. Hydrochloric acid gas is bubbled into the solution for 10 minuntes. The reaction mixture is then sealed, warmed to room temperature and stirred overnight. The solvent is then evaporated to provide 2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-2-cyclohexylacetic acid hydrochloride.

2(R)-[[4-Methoxybenzenesulfonyl](4-picolyl)amino]-cyclohexylacetic acid hydrochloride (1.8g, 4.2 mmol), 1-hydroxybenzotriazole (0.65 g, 4.81 mmol), 4-methyl-morpholine (2.4 mL, 24.04 mmol), and O-t-butylhydroxylamine hydrochloride (1.81 g, 14.4 mmol) are dissolved in methylene chloride (100 mL). N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (1.2 g, 6.25 mmol) is added, and the reaction is stirred overnight. The reaction is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (5% methanol/methylene chloride) to give N-(t-butyloxy)-2-(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-2-cyclohexylacetamide.

(b) Similarly prepared is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-(2-pyridyl)ethyl)amino]-2-cyclohexylacetamide, m.p. 131.5-134.0 °C.

The first two steps are carried out as described above. A Mitsunobu step is substituted for the alkylation step as described below.

To a stirring solution of N-[4-methoxybenzenesulfonyl]-(D)-cyclohexylglycine-t-butyl ester (2.0 g, 5.25 mmol) in tetrahydrofuran (50 mL) is added triphenylphosphine (4.13 g, 15.75 mmol) and 2-(2-hydrox-

yethyl)-pyridine (646.0 mg, 5.25 mmol) followed by diethyl azodicarboxylate (2.28 g, 13.1 mmol). The reaction mixture is stirred at room temperature for 48 hours. The mixture is concentrated directly in vacuo. The crude mixture is applied to a column of silica gel (30% ethylacetate/hexane) to provide t-butyl 2(R)-[N-[4-methoxybenzenesulfonyl](2-(2-pyridyl)ethyl)amino]- 2-cyclohexylacetate.

All of the subsequent steps are carried out as described under (a).

(c) Similarly prepared is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-(3-pyridyl)propyl)amino]-2-cyclohexylacetamide, m.p. 136.0-138 °C, by using 3-pyridinepropanol in the Mitsunobu step, and carrying out the subsequent steps as described above.

(d) Similarly prepared is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-methylpyrid-5-ylmethyl)amino]-2-cyclohexylacetamide, m.p. 156.5-157.0 °C, by using 6-methyl-3-pyridinemethanol (prepared as in J. Org. Chem. 53 3513 (1988)) in the Mitsunobu step, and carrying out the subsequent steps as described above.

(e) Similarly prepared is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-tetrahydropyranmethyl)amino]-2-cyclohexylacetamide, m.p. 75.0-87.0 °C, by using 4-(hydroxymethyl)tetrahydropyran (prepared as in Okrytiya. Izobret. 82 (1985)) in the Mitsunoba step, and carrying out the subsequent steps as described above.

Example 32: N-(t-Butyloxy)-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-N-methylpiperidinyl)-acetamide (733.0 mg, 1.46 mmol) is dissolved in methylene chloride (60 mL) containing ethanol (67.0 mg, 146 mmol), and the reaction is cooled to -10 °C. Hydrochloric acid gas (from a lecture bottle) is bubbled through for 15 minutes. The reaction is sealed, allowed to slowly warm to room temperature, and stirred for 6 days. The solvent is reduced to 1/3 volume by evaporation and triturated with ether. The mixture is filtered, filter cake removed, and dried in vacuo to provide N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)-(benzyl)amino]-2-(4-N-methylpiperidinyl)acetamide hydrochloride as a light tan solid, m.p. >160 °C (dec).

The starting material is prepared as follows:

To a solution of ethyl 4-pyridylacetate (11.17 g, 67.62 mmol) in 2N hydrochloric acid (100 mL) is added platinum (IV) oxide (275 mg). The mixture is shaken in a Parr hydrogenation apparatus for 60 hours under a hydrogen pressure of 50 psi (= 3.45 bar). The reaction mixture is basified to pH 8-9 with saturated aqueous sodium carbonate and then washed with methylene chloride. The aqueous layer is concentrated in vacuo providing sodium 4-piperidyl acetate as a white solid. To a solution of the crude product (5.0 g, 30.3 mmol) in 3:1 water/dioxane (200 mL) at 0 °C is added a solution of di-tert-butyldicarbonate (6.38 g, 29.3 mmol) in dioxane (25 mL) in one portion. The cloudy reaction mixture is warmed to room temperature and stirred overnight. The mixture is then filtered, cooled to 0 °C and acidified with cold 6N hydrochloric acid (pH = 2-3).This solution is extracted with ethyl acetate. The combined organic layers are dried (Na_2SO_4), and the solvent is evaporated to provide N-t-BOC-piperidine-4-acetic acid as a white crystalline solid.

To a solution of N-t-BOC-piperidine-4-acetic acid (4.67 g, 19.22 mmol) in tetrahydrofuran at -78 °C is added triethylamine (2.53 g, 24.99 mmol) followed by pivaloyl chloride (2.55 g, 21.14 mmol). The resulting white slurry is stirred at -78 °C for 15 minutes, warmed to 0 °C for 45 minutes, then recooled to -78 °C. In a separate flask, (R)-(+)-4-benzyl-2-oxazolidinone (4.09 g, 23.1 mmol) is dissolved in tetrahydrofuran (50 mL) and 1M n-butyl lithium in hexanes (14.4 mL, 23.06 mmol) is added dropwise at -78 °C. The solution is added via cannula to the aforementioned white slurry at -78 °C. The reaction mixture is stirred at -78 °C for 15 minutes, then warmed to room temperature over 2.5 hours. The mixture is quenched with saturated aqueous sodium carbonate and the tetrahydrofuran is evaporated in vacuo. The remaining aqueous layer is diluted with water and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated under vacuum. The product is purified by silica gel chromatography (75% to 50% hexane/ethyl acetate) to give 3-[2-(N-t-BOC-4-piperidinyl)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone.

To a solution of 3-[2-(N-t-BOC-4-piperidinyl)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone (7.54 g, 18.76 mmol) in tetrahydrofuran (175 mL) at -78 °C is added a 0.5 M solution of potassium bis (trimethylsilylamide in toluene (37.5 mL, 18.76 mmol) dropwise. After stirring for 20 minutes at -78 °C, a pre-cooled solution of trisylazide (7.25 g, 23.4 mmol) in tetrahydrofuran (55 mL) is added via cannula at -78 °C. The mixture is stirred for 15 minutes at -78 °C, then acetic acid 3.38 g, 56.28 mmol) is added followed by immediate warming to room temperature through immersion in a water bath. The reaction mixture is stirred for 1.5 hours at room temperature. The tetrahydrofuran is removed under vacuum and the resulting residue is partitioned between saturated aqueous sodium carbonate and ethyl acetate. The aqueous layer is removed and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2S0_4), and concentrated in vacuo. The product is purified by silica gel chromatography (30% to 50% ethyl acetate/hexanes) to give 3-[2-(R)-azido-2-(N-t-BOC-4-piperidinyl)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone.

To a solution of 3-[2-(R)-azido-2-(N-BOC-4-piperidinyl)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone (5.84 g, 13.17 mmol) in 3:1 tetrahydrofuran/water/200 mL) at 0 °C is added 30% aqueous hydrogen peroxide (5.12 mL, 52.67 mmol) followed by lithium hydroxide monohydrate (1.11 g, 26.34 mmol). The reaction mixture is stirred at 0 °C for 1 hour. The mixture is quenched by addition of sodium sulfite (7.1 g) at 0 °C. The tetrahydrofuran is removed in vacuo and the remaining aqueous layer is further diluted with water. This aqueous layer is then washed with methylene chloride and acidified with 1N hydrochloric acid. The resulting acidic aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried (Na_2SO_4) and concentrated in vacuo to provide crude 2-(R)-azido-2-(N-t-BOC-4-piperidinyl)acetic acid.

To a pre-stirred solution of tin (II) chloride (3.14 g, 16.55 mmol) in methanol (100 mL) at 0 °C is added 2-(R)-azido-2-(N-t-BOC-4-piperidinyl)acetic acid (2.35 g, 8.27 mmol) in methanol (25 mL) dropwise. The reaction mixture is stirred at 0 °C for 10 minutes then warmed to room temperature overnight. The methanol is removed in vacuo to provide crude R-(N-t-BOC-4-piperidinyl) glycine, which is used directly in the next reaction without purification. The crude product from the above reaction is dissolved in 2:1 dioxane/water (120 mL) and triethylamine (7.53 g, 74.43 mmol) and cooled to 0 °C. To this mixture is added 4-methoxybenzenesulfonyl chloride (2.22 g, 10.75 mmol) and then the reaction mixture is warmed to room temperature overnight. The dioxane is removed in vacuo and the residue is partitioned between dilute aqueous sodium bicarbonate and ethyl acetate. The basic aqueous layer is removed, acidifed with 1N hydrochloric acid, and extracted with ethyl acetate. The resulting emulsion is passed through a celite pad washing with ethyl acetate. The organic filtrate is dried (Na_2SO_4) and concentrated in vacuo to provide 2(R)-[(4-methoxybenzenesulfonyl)amino]-2-(N-t-BOC-4-piperidinyl) acetic acid as crude product.

A solution of crude 2(R)-[(4-methoxybenzenesulfonyl)amino]-2-(N-t-BOC-4-piperidinyl)-acetic acid (2.88 g) in dimethylformamide (60 mL) containing N,N-dicyclohexylamine (1.22 g, 6.73 mmol) and benzyl bromide (1.15 g, 6.73 mmol) is stirred at room temperature for 3.5 hours. To this same reaction mixture is again added benzyl bromide (1.26 g, 7.4 mmol) followed by potassium carbonate (6.5 g, 47.11 mmol). The reaction mixture is stirred over the weekend at room temperature. The mixture is diluted with water and extracted with ethylacetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product is purified by silica gel chromatography (15% to 25% ethyl acetate/hexanes) to provide benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)-amino]-2-(N-t-BOC-4-piperidinyl)acetate.

A solution of benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(N-t-BOC-4-piperidinyl) acetate (2.0 g, 3.3 mmol) in dichloromethane (50 mL) is cooled to 0 °C and hydrochloric acid gas (from a lecture bottle) is bubbled through for 10 minutes. The reaction mixture is warmed to room temperature over 30 minutes. The solvent is removed in vacuo to yield benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(N-t-BOC-4-piperidinyl) acetate hydrochloride as a white foam.

To a solution of benzyl 2(R)-[(4-methoxybenzene sulfonyl)(benzyl)amino]-2-(N-t-BOC-4-piperidinyl) acetate hydrochloride salt (1.28 g, 2.35 mmol) heated to reflux is added sodium formate (480.0 mg, 7.06 mmol) and formaldehyde (0.57 mL, 7.06 mmol). The reaction mixture is refluxed for 10 minutes, then two additional aliquots of formaldehyde (0.57 mL, 7.06 mmol) are added at 10 minute intervals. The reaction mixture is refluxed for an additional 3 hours. The formic acid is removed in vacuo and the residue is partioned between saturated aqueous sodium bicarbonate and ethyl acetate. The basic aqueous layer is further extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4) and concentrated in vacuo to provide benzyl 2(R)-[(4-methoxybenzenesulfonyl)benzyl)amino]-2-(4-N-methyl-piperidinyl) acetate as a crude product. A solution of this crude product (1.23 g) in 3N HCl (40 mL) is refluxed at 120 °C for 2 days. The mixture is concentrated in vacuo to provide acid as a crude product. To a solution of this crude product (1.08 g) in methylene chloride (75 mL) is added 1-hydroxybenzotriazole (0.312 g, 2.31 mmol), 4-methylmorpholine (1.64 g, 16.17 mmol), O-t-butylhydroxylamine hydrochloride (870.0 mg, 6.93 mmol), followed by N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (576.0 mg, 3.0 mmol). The reaction mixture is stirred at room temperature overnight. The reaction is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (3% to 7% methanol/methylene chloride containing 0.5% ammonium hydroxide) to give N-(t-butyloxy)-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-N-methylpiperidinyl)acetamide.

Example 33: Preparation of 3000 capsules each containing 25 mg of the active ingredient, for example, N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride:

Active ingredient	75.00 g
Lactose	750.00 g
Avicel PH 102 (microcrystalline cellulose)	300.00 g
Polyplasdone XL (polyvinylpyrrolidone)	30.00 g
Purified water	q.s.
Magnesium stearate	9.00 g

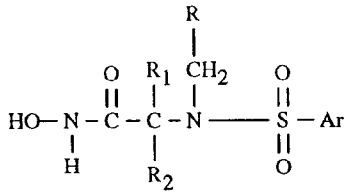
The active ingredient is passed through a No. 30 hand screen.

The active ingredient, lactose, Avicel PH 102 and Polyplasdone XL are blended for 15 minutes in a mixer. The blend is granulated with sufficient water (about 500 mL), dried in an oven at 35 °C overnight, and passed through a No. 20 screen.

Magnesium stearate is passed through a No. 20 screen, added to the granulation mixture, and the mixture is blended for 5 minutes in a mixer. The blend is encapsulated in No. 0 hard gelatin capsules each containing an amount of the blend equivalent to 25 mg of the active ingredient.

Claims

1. A compound of the formula I



(I)

(a) wherein

Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, (carbocyclic or heterocyclic aryl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl or N-lower alkylpiperidyl;

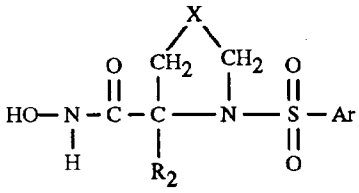
R_2 is hydrogen or lower alkyl;

(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydroisoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxacyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

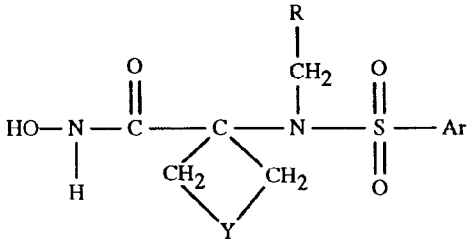
2. A compound according to claim 1 of the formula Ia



(Ia)

wherein X represents methylene or 1,2-ethylene each unsubstituted or substituted by lower alkyl, or X represents oxygen, sulfur, or 1,2-phenylene; Ar and R_2 have meaning as defined in claim 1; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

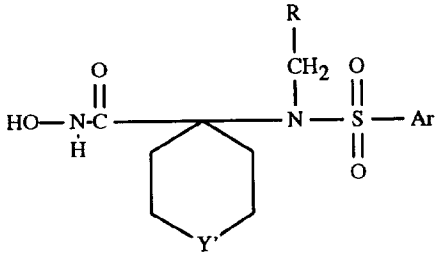
3. A compound according to claim 1 of the formula Ib



(Ib)

wherein Y is a direct bond, C_1-C_4-straight chain alkylene optionally substituted by lower alkyl, CH_2OCH_2, CH_2SCH_2, 1,2-phenylene, CH_2-1,2-phenylene or $CH_2N(R_6)$-CH_2 in which R_6 represents hydrogen, lower alkanoyl, di-lower alkylamino-lower alkanoyl, aroyl, carbocyclic aryl-lower alkanoyl, lower alkyl, carbocyclic or heterocylic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or lower alkylsulfonyl; Ar and R have meaning as defined in claim 1; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3 of the formula Ic



(Ic)

in which Y' represents oxygen, sulfur, a direct bond, methylene or methylene substituted by lower alkyl, or NR_6; R_6 represents hydrogen, lower alkanoyl, di-lower alkylamino-lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkyl, carbocyclic or heterocylic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or lower alkylsulfonyl; Ar and R have meaning as defined in claim 1; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

5. A compound of formula I according to claim 1 wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_{10}-alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; C_3-C_7-cycloalkyl-

lower alkoxy, (lower alkyl, phenyl-lower alkyl or C_3-C_7-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono-or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenylyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluormethyl or cyano; biphenylyl-lower alkyl wherein biphenylyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluormethyl or cyano; (pyridyl, thienyl, quinolinyl or thiazolyl)-lower alkyl, trifluormethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; pyridyl, thienyl, biphenylyl, biphenylyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; trifluoromethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, lower alkanoylamino-lower alkyl; R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl or N-lower alkylpiperidyl;

R_2 is hydrogen or lower alkyl;

(b) or wherein R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydroisoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxacyclohexane, thia-cyclohexane, indane, tetralin and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, benzyloxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

6. A compound of formula I according to claim 1 wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_7-alkoxy, hydroxy, phenyl-lower alkoxy, C_3-C_7-cycloalkyl-lower alkoxy, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy or oxy-C_2-C_3-alkylene; or a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl; biphenylyl; biphenylyl-lower alkyl; (pyridyl or thienyl)-lower alkyl, trifluormethyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-

lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is hydrogen, lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C_1-C_2-alkylenedioxy; biphenylyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, lower alkanoylamino-lower alkyl; R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl or N-lower alkyl-piperidyl;

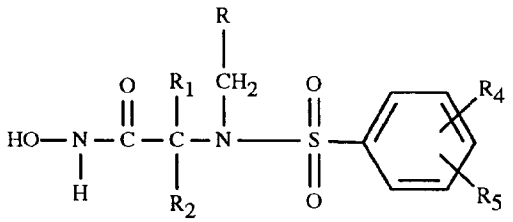
R_2 is hydrogen or lower alkyl;

(b) or wherein R and R_1 together with the chain to which they are attached form a thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R_2 have meaning as defined under (a);

(c) or wherein R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from C_3-C_7-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, aminocarbonyl or mono-or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1 of the formula II



(II)

wherein

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;

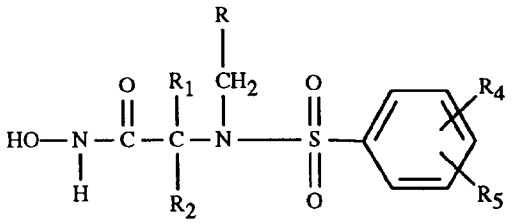
R_1 is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_5-C_7-cycloalkyl, C_5-C_7-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, piperidyl, N-lower alkyl-piperidyl, or acylamino-lower alkyl represented by R_3-CONH-lower alkyl;

R_2 is hydrogen;

R_3 in R_3-CONH-lower alkyl is lower alkyl, carbocyclic or heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower al-

kylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkylpiperidyl)-lower alkyl;
R_4 is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;
R_5 is hydrogen, lower alkyl or halogen;
or R_4 and R_5 together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;
or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

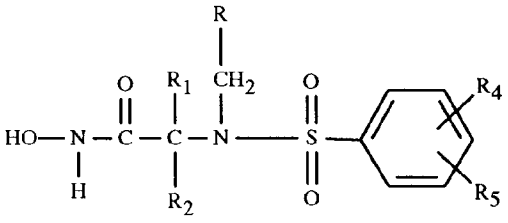
8. A compound according to claim 1 of formula II



(II)

wherein
R and R_1 together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, thiazolidine or pyrrolidine ring;
R_2 is hydrogen;
R_4 is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;
R_5 is hydrogen, lower alkyl or halogen;
or R_4 and R_5 together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;
or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 of formula II

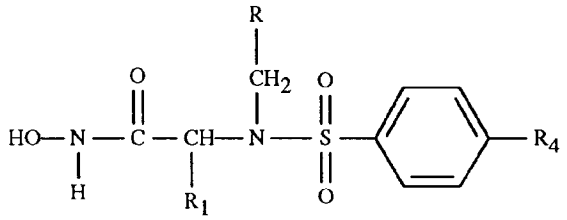


(II)

wherein
R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-lower alkyl, (oxa or thia)-C_3-C_6-cycloalkyl, [(oxa or thia)-C_3-C_6-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;
R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from cyclohexane, cyclopentane, oxacyclohexane, thiacyclohexane, indane, tetralin, piperidine or piperidine

substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl or by lower alkylsulfonyl;
R_4 is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;
R_5 is hydrogen, lower alkyl or halogen;
or R_4 and R_5 together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;
or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 of formula III



(III)

wherein R represents lower alkyl, trifluoromethyl, C_5-C_7-cycloalkyl, (oxa or thia)-C_4-C_5-cycloalkyl, biaryl, carbocyclic monocyclic aryl or heterocyclic monocyclic aryl; R_1 represents hydrogen, lower alkyl, C_5-C_7-cycloalkyl, monocyclic carbocyclic aryl, carbocyclic aryl-lower alkyl, heterocyclic aryl-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, di-lower alkylamino-lower alkyl, (N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino)-lower alkyl or R_3-CONH-lower alkyl; R_3 represents lower alkyl, carbocyclic aryl, heterocyclic aryl, di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkyl-piperidyl)-lower alkyl; R_4 represents lower alkoxy or carbocyclic or heterocyclic aryl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

11. A compound of formula III according to claim 10 wherein R represents heterocyclic monocyclic aryl selected from tetrazolyl, triazolyl, thiazolyl, imidazolyl and pyridyl, each unsubstituted or substituted by lower alkyl; or R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R_1 represents lower alkyl, cyclohexyl, or R_3-CONH-lower alkyl wherein R_3 represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; and R_4 represents lower alkoxy or phenyl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

12. A compound of formula III according to claim 10 wherein R represents 2-, 3- or 4-pyridyl or phenyl; R_1 represents C_1-C_4-alkyl, cyclohexyl or R_3-CONH-C_1-C_4-alkyl wherein R_3 represents di-C_1-C_4-alkylamino-C_1-C_4-lower alkyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

13. A compound of formula III according to claim 10 wherein R represents 3-pyridyl or 4-pyridyl; R_1 represents isopropyl or cyclohexyl; and R_4 represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

14. A compound according to any one of claims 1-13 wherein the asymmetric carbon to which is attached R_1 is assigned the (R)-configuration.

15. A compound according to claim 1 which is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide, a pharmaceutically acceptable prodrug derivative thereof or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 which is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-3-methylbutanamide or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 1 which is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)-amino]-2-cyclohexylacetamide or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 1 which is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-methylpentanamide or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 1 which is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethylglycyl)amino] hexanamide hydrochloride or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19 and a pharmaceutically acceptable carrier.

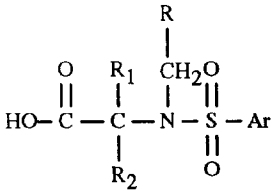
21. A compound according to any one of claims 1 to 19 for use in a method for the therapeutic treatment of the animal or human body.

22. A compound according to any one of claims 1 to 19 for use in the treatment of stromelysin and collagenase dependent conditions.

23. The use of a compound according to any one of claims 1 to 19 for the manufacture of a pharmaceutical composition.

24. The use of a compound according to any one of claims 1 to 19 for the manufacture of a pharmaceutical composition for the treatment of stromelysin and collagenase dependent conditions.

25. A process for the preparation of a compound of formula I according to claim 1, which comprises condensing a carboxylic acid of formula IV,



(IV)

or a reactive functional derivative thereof, wherein R, R_1, R_2 and Ar having meaning as defined in claim 1, with hydroxylamine of formula V,

NH_2-OH (V)

optionally in protected form, or a salt thereof;
and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 81 0896

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	CHEMICAL ABSTRACTS, vol. 59, no. 4, 19 August 1963, Columbus, Ohio, US; abstract no. 3824b, 'N-Arylglycine chemotherapeutics' column 3824 ; * abstract * compound Acetohydroxamic acid, 2-[N-(p-methoxyphenyl)benzenesulfonamido]- & YAKUGAKU ZASSHI vol. 83 , 1963 pages 130 - 134 KAORU KONDO ET AL	1-25	C07D213/42 C07C311/29 C07D317/62 C07D317/58 C07D405/14 C07D277/28 C07D215/12 C07D277/06 C07D207/48 C07D277/30 A61K31/44 A61K31/18
A	US-A-4 885 027 (P.B. POMIDOR) 5 December 1989 *see formula I, especially definitions of R and R1*	1-25	
A	TRENDS BIOTECHNOL. vol. 10, no. 6 , 1992 , UK pages 200 - 207 A.J.P.DOCHERTY ET AL 'The matrix metalloproteinases and their natural inhibitors: prospects for treating degenerative tissue disease'	1-25	TECHNICAL FIELDS SEARCHED (Int.Cl.5) C07D C07C A61K
A	WO-A-90 05719 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 *see formula I and whole document*	1-25	
A	EP-A-0 236 872 (F.HOFFMANN-LA ROCHE & CO) 16 September 1987 * the whole document *	1-25	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	17 March 1994	Scruton-Evans, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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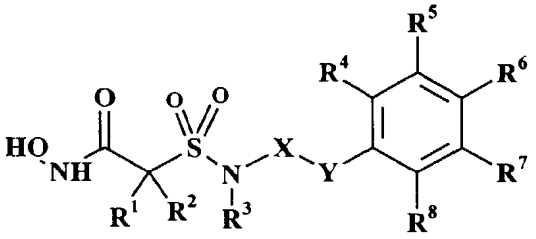
(54) Metalloprotease inhibitors

(57) Compounds of formula (I):



(I)

where the substituents are as defined herein, and salts thereof, are matrix metalloprotease inhibitors.

EP 0 931 788 A2

Description

[0001] This invention relates to a series of substituted α-aminosulphonyl-acetohydroxamic acids which are inhibitors of zinc-dependent metalloprotease enzymes. In particular, the compounds are inhibitors of certain members of the matrix metalloprotease (MMP) family.

[0002] Matrix metalloproteases (MMPs) constitute a family of structurally similar zinc-containing metalloproteases, which are involved in the remodelling and degradation of extracellular matrix proteins, both as part of normal physiological processes and in pathological conditions. Since they have high destructive potential, MMPs are usually under close regulation and failure to maintain MMP regulation has been implicated as a component of a number of diseases and conditions including pathological conditions, such as atherosclerotic plaque rupture, heart failure, restenosis, periodontal disease, tissue ulceration, wound repair, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

[0003] Another important function of certain MMPs is to activate various enzymes, including other MMPs, by cleaving the pro-domains from their protease domains. Thus some MMPs act to regulate the activities of other MMPs, so that over-production of one MMP may lead to excessive proteolysis of extracellular matrix by another. Moreover, MMPs have different substrate preferences (shown in the following Table for selected family members) and different functions within normal and pathological conditions. For recent reviews of MMPs, see Current Pharmaceutical Design, 1996, 2, 624 and Exp. Opin. Ther. Patents, 1996, 6, 1305.

TABLE

Enzyme	Other Names	Preferred Substrates
MMP-1	collagenase-1; interstitial collagenase	collagens I, II, III, VII, X; gelatins
MMP-2	gelatinase A; 72kDa gelatinase	gelatins; collagens IV, V, VII, X; elastin; fibronectin; activates pro-MMP-13
MMP-3	stromelysin-1	proteoglycans; laminin; fibronectin; gelatins
MMP-8	collagenase-2; neutrophil collagenase	collagens I, II, III
MMP-9	gelatinase B; 92kDa gelatinase	gelatins; collagens IV, V; elastin
MMP-13	collagenase-3	collagens I, II, III; gelatins
MMP-14	MT-MMP-1	activates pro-MMP-2 & 13; gelatins

[0004] Excessive production of MMP-3 is thought to be responsible for pathological tissue breakdown which underlies a number of diseases and conditions. For example, MMP-3 has been found in the synovium and cartilage of osteoarthritis and rheumatoid arthritis patients, thus implicating MMP-3 in the joint damage caused by these diseases: see Biochemistry, 1989, 28, 8691 and Biochem. J., 1989, 258, 115. MMP-13 is also thought to play an important role in the pathology of osteoarthritis and rheumatoid arthritis: see Lab. Invest., 1997, 76, 717 and Arthritis Rheum., 1997, 40, 1391. The compounds of the present invention inhibit both MMP-3 and MMP-13 and thus may be of utility in treating these diseases.

[0005] The over-expression of MMP-3 has also been implicated in the tissue damage and chronicity of chronic wounds, such as venous ulcers, diabetic ulcers and pressure sores: see Brit. J. Dermatology, 1996, 135, 52.

[0006] Furthermore, , the production of MMP-3 may also cause tissue damage in conditions where there is ulceration of the colon (as in ulcerative colitis and Crohn's disease: see J. Immunol., 1997 158, 1582 and J. Clin. Pathol., 1994, 47, 113) or of the duodenum (see Am. J. Pathol., 1996, 148, 519).

[0007] Moreover, MMP-3 is also thought to be involved in skin diseases such as dystrophic epidermolysis bullosa (see Arch. Dermatol. Res., 1995, 287, 428) and dermatitis herpetiformis (see J. Invest. Dermatology, , 1995, 105, 184).

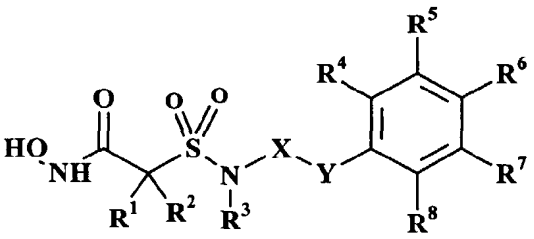
[0008] Rupture of atherosclerotic plaques by MMP-3 has also been described (see e.g. Circulation, 1997, 96, 396). Thus, MMP-3 inhibitors may find utility in the treatment of conditions caused by or complicated by embolic phenomena such as cardiac or cerebral infarctions.

[0009] Studies of human cancers have shown that MMP-2 is activated on the invasive tumour cell surface (see J. Biol.Chem., 1993, 268, 14033) and BB-94, a non-selective peptidic hydroxamate MMP inhibitor, has been reported to decrease the tumour burden and prolong the survival of mice carrying human ovarian carcinoma xenografts (see Cancer Res., 1993, 53, 2087). Certain compounds of the present invention inhibit MMP-2 and therefore may be useful in the treatment of cancer metastasis and tumour angiogenesis.

[0010] Various series of MMP inhibitors have appeared in the literature which have a carbonyl moiety (CO) and a sulphone moiety (SO_2) with a two atom "spacer" interposed between them. For example, α-arylsulphonamido-substituted acetohydroxamic acids are disclosed in EP-A-0606046, WO-A-9627583 and WO-A-9719068, whilst EP-A-0780386 discloses certain related sulphone-substituted hydroxamic acids.

[0011] The compounds of the present invention represent a new class of compounds, and are inhibitors of some of the members of the MMP family. In particular, they are potent inhibitors of MMP-3 and MMP-13, with certain compounds exhibiting varying degrees of selectivity over other MMPs, such as MMP-1, MMP-2 and MMP-9. Certain of the compounds are potent MMP-2 inhibitors.

[0012] Thus, according to one aspect of the present invention, there is provided a compound of formula (I):



(I)

and a pharmaceutically- and/or veterinarily-acceptable salt thereof, and a solvate of such compound and salt, wherein

R^1 and R^2 are each independently H,
C_{2-6} alkenyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl), aryloxy(C_{1-6} alkyl), heteroaryloxy(C_{1-6} alkyl),
C_{1-6} alkyl optionally substituted by NH_2, C_{2-6} acylamino, OH, or by CO_2H,
or R^1 and R^2 can be taken together with the carbon atom to which they are attached, to form a 4- to 8-membered saturated carbocyclic or heterocyclic ring, which heterocyclic ring has 1 or 2 hetero-groups selected from O, $S(O)_n$ or NR^9 in the ring,
R^3 is H, C_{1-6} alkyl or (C_{1-6} alkoxy)C_{1-6} alkyl,
R^4, R^5, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^6 is H, aryl, heteroaryl, aryloxy or heteroaryloxy, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^9 is H or C_{1-6} alkyl,
n is 0,1 or 2,
X is C_{1-6} alkylene or C_{2-6} alkenylene,
Y is a direct link, CH=CH or O,

wherein "aryl" is phenyl optionally fused with another ring selected from furan, dioxolan, and pyran,
which group is optionally mono- or disubstituted by substituents independently seleceted from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy),
and wherein "heteroaryl" is a 5- or 6-membered aromatic heterocycle with one or two heteroatoms in the ring, which heteroatoms are independently selected from O, N and S, which heteroaryl is optionally mono- or disubstituted by substituents independently selected from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy).

[0013] In the above definition, unless otherwise indicated, alkyl, alkenyl, alkylene and alkenylene groups having three or more carbon atoms may be straight chain or branched chain.

[0014] The compounds of formula (I) may contain one or more chiral centres and therefore can exist as stereoisomers, i.e. as enantiomers or diastereoisomers, as well as mixtures thereof. The invention includes both the individual stereoisomers of the compounds of formula (I) and any mixture thereof. Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation or chromatography (including HPLC) of a diastereoisomeric mixture of a compound of formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of formula (I) may be prepared from a corresponding optically pure intermediate or by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active base or acid, as appropriate to the

specific compound to be resolved. Furthermore, compound of formula (I) which contain alkenyl groups can exist as *cis*- or *trans*- geometric isomers. Again, the invention includes both the separated individual geometric isomers as well as mixtures thereof.

[0015] Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

[0016] The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

[0017] Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

[0018] Suitable base salts are formed from bases which form non-toxic salts and examples are the aluminum, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

[0019] For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

Preferably R^1 is H.

Preferably R^2 is H.

Preferably R^3 is H or C_{1-6} alkyl.
More preferably R^3 is H or CH_3.

Preferably R^4 is H.

Preferably R^5 is H or C_{1-6} alkyl.
More preferably $R^5$is H or CH_3.

Preferably R^6 is H, $aryl^1$ or $aryl^1$oxy wherein "$aryl^1$" is phenyl optionally mono- or disubstituted by substituents selected from halogen and CN.
More preferably R^6 is H, $aryl^2$ or $aryl^2$oxy wherein "$aryl^2$" is phenyl optionally 4-substituted by substituents selected from Cl and CN.
Most preferably R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl.

Preferably R^7 is H.

Preferably R^8 is H.

Preferably X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or is $CH_2CH{=}CH$ wherein the terminal methinyl carbon of this group is linked to the Y moiety.

[0020] A preferred group of compounds, salts and solvates is that in which at least two of the groups R^4, R^5, R^7 and R^8 are all H.

[0021] Another preferred group of compounds, salts and solvates is that in which R^4, R^7 and R^8 are all H and R^5 is CH_3.

[0022] Yet another preferred group of compounds, salts and solvates is that in which R^1,R^2, R^4, R^7 and R^8 are all H,
R^3 is H or CH_3,
$R^5$is H or CH_3,
R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl,
X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or $CH_2CH{=}CH$,
and the salts and solvates thereof.

[0023] The most preferred compounds, , salts and solvates are those of the Examples and the salts and solvates thereof.

[0024] The invention further provides synthetic methods for the production of compounds, salts and solvates of the invention, which are described below and in the Examples. The skilled man will appreciate that the compounds, salts and solvates of the invention could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example the art described herein.

[0025] In the Methods below, unless otherwise specified, the substituents are as defined above with reference to the compounds of formula (I).

[0026] Where desired or necessary, the compound of formula (I) can be converted into a pharmaceutically or veterinarily acceptable salt thereof, conveniently by mixing together solutions of a compound of formula (I) and the desired acid or base, as appropriate. The salt may be precipitated from solution and collected by filtration, or may be collected by other means such as by evaporation of the solvent. In some cases, the salt may be the direct product of a reaction to make a compound or salt of the invention in a solvent, in which case no further transformation step would be necessary.

[0027] Where desired or necessary, solvates of the compounds and salts of the invention may be made by standard methods well known in the art. In some cases, the solvate may be the direct product of a reaction to make a compound or salt of the invention, in which case no further transformation step would be necessary.

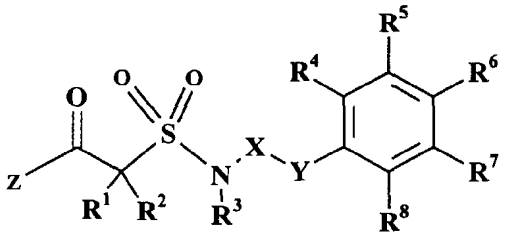
[0028] It is to be understood that the synthetic transformation methods mentioned herein may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound.

[0029] It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional methods, for example as described in "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley & Sons Inc (1991).

[0030] The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

[0031] Unless otherwise stated, the substituents of the intermediates described below are as defined above for formula (I).

[0032] A compound of formula (I) may be prepared directly from an acid derivative of formula (II):



(II)

where Z is chloro, bromo, iodo, C_{1-3} alkyloxy or HO.

[0033] When prepared directly from the ester of formula (II), where Z is C_{1-3} alkyloxy, the reaction may be carried out by treatment of the ester with hydroxylamine, preferably up to a 3-fold excess of hydroxylamine, in a suitable solvent at from about room temperature to about 85°C. The hydroxylamine is conveniently generated in situ from a suitable salt such as its hydrochloride salt by conducting the reaction in the presence of a suitable base such as an alkali metal carbonate or bicarbonate, e.g. potassium carbonate. Preferably the solvent is a mixture of methanol and tetrahydrofuran and the reaction is temperature is from about 65 to 70°C.

[0034] Alternatively, the ester (II, where Z is C_{1-3} alkyloxy) may be converted by conventional hydrolysis to the corresponding carboxylic acid (II, Z is HO) which is then transformed to the required hydroxamic acid of formula (I).

[0035] Preferably the hydrolysis of the ester is effected under basic conditions using up to about a 6-fold excess of an alkali metal hydroxide in aqueous solution, optionally in the presence of a co-solvent, at from about room temperature to about 85°C. Typically the co-solvent is a mixture of methanol and tetrahydrofuran or a mixture of methanol and 1,4-dioxan and the reaction temperature is from about 40 to about 70°C.

[0036] The subsequent coupling step may be achieved using conventional amide-bond forming techniques, e.g. via the acyl halide derivative (II, Z is Cl, I or Br) and hydroxylamine hydrochloride in the presence of an excess of a tertiary amine such as triethylamine or pyridine to act as acid-scavenger, optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in a suitable solvent such as dichloromethane, at from about 0°C to about room temperature. For convenience, pyridine may also be used as the solvent.

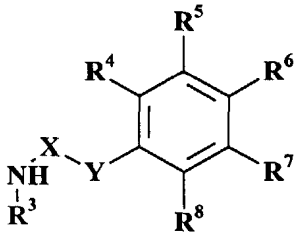
[0037] In particular, any one of a host of amino acid coupling variations may be used. For example, the acid of formula (II) wherein Z is HO may be activated using a carbodiimide such as 1 ,3-dicyclohexylcarbodiimide or 1 -ethyl-3-(3-dimethylaminoprop-1-yl)carbodiimide optionally in the presence of 1 -hydroxybenzotriazole and/or a catalyst such as 4-dimethylaminopyridine, or by using a halotrisaminophosphonium salt such as bromotris(pyrrolidino)-phosphonium hex-

afluorophosphate. Either type of coupling is conducted in a suitable solvent such as dichloromethane or dimethylformamide, optionally in the presence of a tertiary amine such as N-methylmorpholine or N-ethyldiisopropylamine (for example when either the hydroxylamine or the activating reagent is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Typically, from 1.1 to 2.0 molecular equivalents of the activating reagent and from 1.0 to 4.0 molecular equivalents of any tertiary amine present are employed.

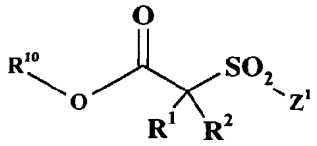
[0038] A preferred reagent for mediating the coupling reaction is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).

[0039] Preferably a solution of the acid (II, Z is HO) and N-ethyldiisopropylamine in a suitable solvent such as anhydrous dimethylformamide or anhydrous 1-methylpyrrolidin-2-one, under nitrogen, is treated with up to a 1.5-fold excess of HATU at about room temperature followed, after about 15 to 30 minutes, with up to about a 3-fold excess of hydroxylamine hydrochloride and up to about a 4-fold excess of N-ethyldiisopropylamine, optionally in the same solvent, at the same temperature.

[0040] An ester of formula (II, Z is C_{1-3} alkyloxy) may be prepared from an amine of formula (III) by sulphonylation with a compound of formula (IV), wherein R^{10} is C_{1-3} alkyloxy and Z^1 is a leaving group such as Br, I or Cl.



(III)



(IV)

Preferably, Z^1 is chloro.

[0041] The reaction may be effected in the presence of an appropriate base in a suitable solvent at from about 0°C to about room temperature. For example, when both R^1 and R^2 are hydrogen, an appropriate base is 1,8-diazabicyclo[5.4.0]undec-7-ene and a suitable solvent is dichloromethane.

[0042] Certain esters of formula (II, Z is C_{1-3} alkyloxy) wherein at least one of R^1 and R^2 is other than hydrogen may be conveniently obtained from the α-carbanion of an ester of formula (II) wherein at least one of R^1 and R^2 is hydrogen by conventional C-alkylation procedures using an alkylating agent of formula (VA) or (VB):

(VA) (VB)

wherein R is as previously defined for R^1 or R^2 but is not hydrogen, Z^2 and Z^3 may be the same or different and are suitable leaving groups such as chloro, bromo, iodo, C_1-C_4 alkanesulphonyloxy, trifluoromethanesulphonyloxy or arylsulphonyloxy (e.g. benzenesulphonyloxy or p-toluenesulphonyloxy), and q is 3, 4, 5, 6 or 7.

[0043] Preferably, Z^2 and Z^3 are selected from bromo, iodo and p-toluenesulphonyloxy.

[0044] The carbanion may be generate using an appropriate base in a suitable solvent. Typical base-solvent combinations may be selected from lithium, sodium or potassium hydride, lithium, sodium or potassium bis(trimethylsilyl)amide, lithium diisopropylamide and butyllithium, together with toluene, ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxan, dimethylformamide, N,N-dimethylacetamide, 1-methylpyrrolidin-2-one and any mixture thereof.

[0045] Preferably the base is sodium hydride and the solvent is dimethylformamide, optionally with tetrahydrofuran as co-solvent, or 1-methylpyrrolidin-2-one. For monoalkylation up to about a 10% excess of base is employed whilst, for dialkylation, from about 2 to about 3 molar equivalents are generally appropriate.

[0046] Typically, the carbanion is generated at about room temperature, under nitrogen, and subsequently treated with the required alkylating agent at the same temperature. Clearly, when dialkylation is required and R^1 and R^2 are different, the substituents may be introduced in tandem in a "one-pot reaction" or in separate steps.

[0047] An amine of formula (III) may be obtained by standard chemical procedures. Other amines of formula (III),

when neither commercially available nor subsequently described, can be obtained either by analogy with the processes described in the Preparations section below or by conventional synthetic procedures, in accordance with standard textbooks on organic chemistry or literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

[0048] Moreover, persons skilled in the art will be aware of variations of, and alternatives to, those processes described hereinafter in the Examples and Preparations sections which allow the compounds defined by formula (I) to be obtained.

[0049] The biological activities of the compounds of the present invention were determined by the following test methods, which are based on the ability of the compounds to inhibit the cleavage of various fluorogenic peptides by MMPs 1, 2, 3, 9, 13 and 14.

[0050] The assays for MMPs 2, 3, 9 and 14 are based upon the original protocol described in fed.Euro.Biochem.Soc., 1992, 296, 263, with the minor modifications described below.

Inhibition of MMP-1

Enzyme Preparation

[0051] Catalytic domain MMP-1 was prepared in Pfizer Central Research laboratories. A stock solution of MMP-1(1μM) was activiated by the addition of aminophenylmercuric acetate (APMA), at a final concentration of 1mM, for 20 minutes at 37°C. MMP-1 was then diluted in Tris-HCl assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnSO_4$ and 0.05% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

Substrate

[0052] The fluorogenic substrate used in this assay was Dnp-Pro-β-cyclohexyl-Ala-Gly-Cys(Me)-His-Ala-Lys-(N-Me-Ala)-NH_2 as originally described in Anal. Biochem., 1993, 212, 58. The final substrate concentration used in the assay was 10μM.

Determination of Enzyme Inhibition

[0053] The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence (substrate cleavage) using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 355 nm and emission wavelength of 440 nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-2, MMP-3 and MMP-9

Enzyme Preparation

[0054] Catalytic domains MMP-2, MMP-3 and MMP-9 were prepared in Pfizer Central Research laboratories. A stock solution of MMP-2, MMP-3 or MMP-9 (1μM) was activated by the addition of APMA. For MMP-2 and MMP-9, a final concentration of 1mM APMA was added, followed by incubation for 1 hour at 37°C. MMP-3 was activated by the addition of 2mM APMA, followed by incubation for 3 hours at 37°C. The enzymes were then diluted in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM $CaCl_2$ and 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assays was 1nM.

Substrate

[0055] The fluorogenic substrate used in this screen was Mca-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2 (Bachem Ltd., Essex, UK) as originally described in J.Biol.Chem., 1994, 269 20952. This substrate was selected because it has a balanced hydrolysis rate against MMPs 2, 3 and 9 (k_{cat}/k_m of 54,000, 59,400 and 55,300 $^{s-1}$ M^{-1} respectively). The final substrate concentration used in the assay was 5μM.

Determination of Enzyme Inhibition

[0056] The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C, prior to determination of fluorescence using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 328nm and emission wavelength of 393nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-13

Enzyme Preparation

[0057] Human recombinant MMP-13 was prepared by PanVera Corporation (Madison, Wisconsin) and characterised at Pfizer Central Research laboratories. A 1.9 mg/ml stock solution was activated with 2mM APMA for 2 hours at 37°C. MMP-13 was then diluted in assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnCl_2$ and 0.02% Brij 35, pH 7.5) to a concentration of 5.3nM. The final concentration of enzyme used in the assay was 1.3nM.

Substrate

[0058] The fluorogenic substrate used in this screen was Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2. The final substrate concentration used in the assay was 10μM.

Determination of Enzyme Inhibition

[0059] The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate. The addition of substrate to each well initiated the reaction. Fluorescence intensity was determined using a 96 well plate fluorimeter (Cytofluor II; PerSeptive Biosystems, Inc., Framingham, MA) at an excitation wavelength of 360nm and emission wavelength of 460nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-14

Enzyme Preparation

[0060] Catalytic domain MMP-14 was prepared in Pfizer Central Research laboratories. A 10μM enzyme stock solution was activated for 20 minutes at 25°C following the addition of 5μg/ml of trypsin (Sigma, Dorset, UK). The trypsin activity was then neutralised by the addition of 50μg/ml of soyabean trypsin inhibitor (Sigma, Dorset, UK), prior to dilution of this enzyme stock solution in Tris-HCl assay buffer (100mM Tris, 100nM NaCl, 10mM $CaCl_2$, 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

Substrate

[0061] The fluorogenic substrate used in this screen was Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 (Bachem Ltd., Essex, UK) as described in J.Biol.Chem. 1996, 271, 17119.

Determination of enzyme inhibition

[0062] This was performed as described for MMPs 2, 3 and 9.

[0063] For use in mammals, including humans, the compounds of formula (I) or their salts or solvates of such compounds or salts, can be administered alone, but will generally be administered in admixture with a pharmaceutically or veterinarily acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the

form of elixirs, solutions or suspensions containing flavouring or colouring agents. The compound or salt could be incorporated into capsules or tablets for targetting the colon or duodenum via delayed dissolution of said capsules or tablets for a particular time following oral administration. Dissolution could be controlled by susceptibility of the formulation to bacteria found in the dudodenum or colon, so that no substantial dissolution takes places before reaching the target area of the gastrointestinal tract. The compounds or salts can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution or suspension which may contain other substances, for example, enough salt or glucose to make the solution isotonic with blood. They can be administered topically, in the form of sterile creams, gels, suspensions, lotions, ointments, dusting powders, sprays, drug-incorporated dressings or via a skin patch. For example they can be incorporated into a cream consisting of an aqueous or oily emulsion of polyethylene glycols or liquid paraffin, or they can be incorporated into an ointment consisting of a white wax soft paraffin base, or as hydrogel with cellulose or polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA or CFC propellants, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycols impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings. The compound or salt could also be administered intraocularly as an eye drop with appropriate buffers, viscosity modifiers (e.g. cellulose derivatives), preservatives (e.g. benzalkonium chloride (BZK)) and agents to adjust tenicity (e.g. sodium chloride). Such formulation techniques are well-known in the art.

[0064] For veterinary use, a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

[0065] All such formulations may also contain appropriate stabilisers and preservatives.

[0066] Reference to treatment includes prophylaxis as well as alleviation of established conditions, or the symptoms thereof.

[0067] For oral and parenteral administration to animal (inc. human) patients, the daily dosage level of the compounds of formula (I) or their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.1 to 10, and most preferably from 0.5 to 5 mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time as appropriate.

[0068] For topical administration to animal (inc. human) patients with chronic wounds, the daily dosage level of the compounds, in suspension or other formulation, could be from 0.00001 to 1mg/ml, preferably from 0.001 to 0.1 mg/ml.

[0069] The physician or veterinary surgeon in any event will determine the actual dosage which will be most suitable for a an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can of course be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0070] Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate of either entity, together with a pharmaceutically acceptable diluent or carrier.

[0071] It further provides a veterinary formulation comprising a compound of formula (I), or a veterinarily acceptable salt thereof or a veterinarily acceptable solvate of either entity, together with a veterinarily acceptable diluent or carrier.

[0072] The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing, for use as a human medicament.

[0073] In addition, it provides a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, or a veterinary formulation containing any of the foregoing, for use as a medicament for non-human animal.

[0074] In yet another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the treatment of a condition mediated by one or more MMPs.

[0075] It also provides the use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, for the manufacture of an animal medicament for the treatment of a condition mediated by one or more MMPs.

[0076] Moreover, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

[0077] It also provides the use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate containing either entity, for the manufacture of an animal medicament for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

[0078] Additionally, the invention provides a method of treating or preventing a medical condition for which a MMP inhibitor is indicated, in an animal such as a mammal (including a human being), which comprises administering to said animal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing.

[0079] Still further, the invention provides a method of treating or preventing atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells, in a animal (including a human being), which comprises administering to said animal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing.

[0080] The invention also includes any novel intermediates described herein, for example those of formula (II).

[0081] The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations.

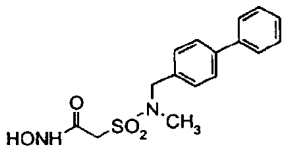
EXAMPLES AND PREPARATIONS

[0082] Room temperature means 20 to 25°C. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh). Melting points are uncorrected. ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AC300, a Varian Unity Inova-300 or a Varian Unity Inova-400 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded using a Finnigan Mat. TSQ 7000 or a Fisons Instruments Trio 1000 mass spectrometer. LRMS means low resolution mass spectrum and the calculated and observed ions quoted refer to the isotopic composition of lowest mass._Hexane refers to a mixture of hexanes (hplc grade) b.p. 65-70°C. Ether refers to diethyl ether. Acetic acid refers to glacial acetic acid. 1-Hydroxy-7-aza- 1H-1,2,3-benzotriazole (HOAt), *N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-*b*]pyridin- 1-ylmethylene]-*N*-methylmethaninium hexafluorophosphate *N*-oxide (HATU) and 7-azabenzotriazol-1-yloxy*tris*(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) were purchased from PerSeptive Biosystems U.K. Ltd.

Example 1

N-Hydroxy 2-({methyl[(biphen-4-yl)methyl]amino}sulfonyl)acetamide

[0083]



(a) Methyl 2-({methyl[(biphen-4-yl)methyl]amino}sulfonyl)acetate

[0084] *N*-Methyl-*N*-[(biphen-4-yl)methyl]amine (Preparation 1, 500 mg, 2.5 mmol) and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU, 0.38 ml, 2.5 mmol) were dissolved in dichloromethane (5 ml) and cooled to 0°C. Methyl chlorosulfonylacetate (0.44 g, 2.5 mmol) in dichloromethane (5 ml) was added dropwise to the solution, and the stirred mixture was allowed to warm to ambient temperature for 20 hours. The mixture was diluted with dichloromethane and washed with aqueous phosphate buffer (at pH 7), dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The

residue was purified by flash chromatography on silica gel (dichloromethane as eluent) and the isolated product was crystallised from diisopropyl ether to give the title compound as a colourless solid (388 mg).

m.p. 82-84°C
^{1}H NMR (400 MHz, $CDCl_3$): 2.90 (s, 3H), 3.86 (s, 3H), 4.05 (s, 2H), 4.46 (s, 2H), 7.33-7.40 (m, 1H), 7.40-7.45 (m, 4H), 7.54-7.67 (m, 4H).
LPMS (Thermospray): 334.8 (MH^+).

(b) *N*-Hydroxy-2-({methyl[(biphen-4-yl)methyl]amino}sulfonyl)acetamide

[0085] Potassium carbonate (124 mg, 0.9 mmol) was added to a mixture of methyl 2-({methyl[(biphen-4-yl)methyl]amino}sulfonyl)acetate (100 mg, 0.3 mmol) and hydroxylamine hydrochloride (63 mg, 0.9 mmol) in methanol (3 ml). The mixture was heated to reflux for 18 hours. The mixture was cooled and partitioned between ethyl acetate and 0.1M aqueous hydrochloric acid. The layers were separated, and the organic layer was dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was triturated with diisopropyl ether to give the titled compound as a colourless solid (88 mg).

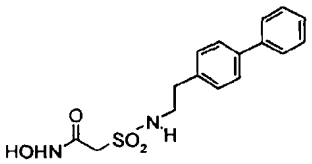
m.p. 176-178°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.75 (s, 3H), 3.98 (s, 2H), 4.33 (s, 2H), 7.33-7.52 (m, 5H), 7.61-7.74 (m, 4H), 9.22 (s, 1H), 10.84 (br s, 1H).
LRMS (Thermospray): 335.7 (MH^+)

Analysis:	Found:	C, 57.32;	H, 5.40;	N, 8.24.
$C_{16}H_{18}N_2O_4S$	Requires:	C, 57.47;	H, 5.43;	N, 8.38.

Example 2

N-Hydroxy 2-({[2-(biphen-4-yl]ethyl]amino} sulfonyl)acetamide

[0086]



(a) Methyl 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetate

[0087] In a manner similar to Example 1 (a), 2-(biphen-4-yl)ethylamine (Preparation 2) was reacted with methyl chlorosulfonylacetate to give the title compound as a colourless solid.

m.p. 130-131°C
^{1}H NMR (300 MHz, $CDCl_3$): 2.97 (t, 2H), 3.49 (q, 2H), 3.76 (s, 3H), 3.93 (s, 2H), 4.76 (br t, 1H), 7.22-7.40 (m, 3H), 7.40-7.50 (m, 2H), 7.52-7.64 (m, 4H).
LRMS (Thermospray): 351.1 (MNH_4^+)

Analysis:	Found:	C, 61.39;	H, 5.74;	N, 4.19.
$C_{17}H_{19}NO_4S$,	Requires:	C, 61.24;	H, 5.74;	N, 4.20.

(b) *N*-Hydroxy 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetamide

[0088] In a manner similar to Example 1 (b), methyl 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

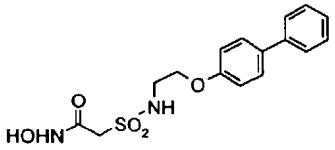
m.p. 202-204°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.81 (t, 2H), 3.16-3.29 (m, 2H), 3.78 (s, 2H), 7.24-7.39 (m, 3H), 7.40-7.50 (m, 2H), 7.54-7.68 (m, 4H), 9.13 (s, 1H), 10.74 (br s, 1H).
LRMS (Thermospray): 336.2 (MH^+)

Analysis:	Found:	C, 57.45;	H, 5.40;	N, 8.35.
$C_{16}H_{18}N_2O_4S$	Requires:	C, 57.47;	H, 5.43;	N, 8.38.

Example 3

N-Hydroxy 2-({[2-(biphen-4-yloxy)ethyl]amino} sulfonyl)acetamide

[0089]



(a) Methyl 2-({[2(biphen-4-yloxy)ethyl]amino}sulfonyl)acetate

[0090] In a manner similar to Example 1 (a), 2-(biphen-4-yloxy)ethylamine (Preparation 3) was reacted with methyl chlorosulfonylacetate to give the title compound as a colourless solid.

m.p. 123-124°C
^{1}H NMR (400 MHz, $CDCl_3$): 3.62 (q, 2H), 3,79 (s, 3H), 4.10 (s, 2H), 4.18 (t, 2H), 5.26 (br t, 1H), 6.98 (d, 2H), 7.31-7.34 (m, 1H), 7.39-7.46 (m, 2H), 7.50-7.60 (m, 4H).

Analysis:	Found:	C, 58.33;	H, 5.44;	N, 3.99.
$C_{17}H_{19}NO_5S$	Requires:	C, 58.43;	H, 5.48;	N, 4.01.

(b) *N*-Hydroxy 2-({[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetamide

[0091] In a manner similar to Example 1 (b), methyl 2-({[2-(biphen-4yloxy)ethyl]amino} sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

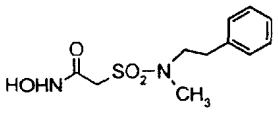
m.p. 222-224°C
^{1}H NMR (400 MHz, DMSO-d_6): 3.39 (d, 2H), 3.86 (s, 2H), 4.07 (t, 2H), 7.07 (d, 2H), 7.29-7.33 (m, 1H), 7.37-7.51 (m, 3H), 7.57-7.65 (m, 4H), 9.13 (s, 1H), 10.73 (s, 1H).
LPMS (Thermospray): 352.0 (MH^+)

Analysis:	Found:	C, 54.69;	H, 5.13;	N, 7.92.
$C_{19}H_{22}N_2O_4S$	Requires:	C, 54.84;	H, 5.18;	N, 8.00.

Example 4

N-Hydroxy 2-[methyl(phenethyl)amino]sulfonylacetamide

[0092]



(a) Methyl 2-[methyl(phenethyl)amino]sulfonylacetate

[0093] In a manner similar to Example 1 (a), *N*-methyl-*N*-phenethylamine was reacted with methyl chlorosulfonylacetate to give the titled compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 2.88-2.96 (m, 5H), 3.48 (t, 2H), 3.77 (s, 3H), 3.81 (s, 2H), 7.18-7.36 (m, 5H).

(b) *N*-Hydroxy 2-[methyl(phenethyl)amino]sulfonylacetamide

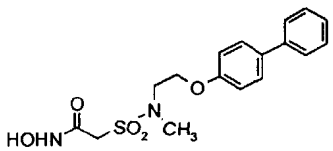
[0094] In a manner similar to Example 1 (b), methyl 2-[methyl(phenethyl)amino]sulfonylacetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 149-151°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.76-2.86 (m, 5H), 3.28 (s, 2H), 3.80 (s, 2H), 7.15-7.35 (m, 5H), 9.14 (s, 1H), 10.73 (s, 1H).
LRMS (Thermospray): 290.0 (MNH_4^+)
$C_{11}H_{16}N_2O_4S$.

Example 5

N-Hydroxy 2-({methyl-[2-(biphen-4-yloxy)ethyl]amino} sulfonyl)acetamide

[0095]



(a) Methyl 2-({methyl-[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetate

[0096] Sodium hydride (23 mg of 60% dispersion in mineral oil, 0.58 mmol) was added to a stirred solution of methyl 2-({[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetate (Example 3(a), 185 mg, 0.53 mmol) in anhydrous dimethylforma-

mide (2 ml) at ambient temperature under a nitrogen atmosphere. After 30 minutes methyl *p*-toluenesulfonate (0.99 g, 0.53 mmol) was added, and stirring continued for an additional 3 hours. The mixture was partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The organic layer was separated and washed with water, dried ($MgSO_4$) and the solvents were removed under reduced pressure. The residue was crystallised from diisopropyl ether to give the titled compound as a colourless solid (170 mg).

m.p. 73-75°C
^{1}H NMR (400 MHz, $CDCl_3$): d = 3.11 (s, 3H), 3.69 (t, 2H), 3,78 (s, 3H), 4.08 (s, 2H), 4.18 (t, 2H), 6.97 (d, 2H), 7.28-7.32 (m, 1H), 7.38-7.46 (m, 2H), 7.47-7.58 (m, 4H).
LRMS (Thermospray): 381.1 (MNH_4^+)

Analysis:	Found:	C, 59.39;	H, 5.88;	N, 3.74.
$C_{18}H_{21}NO_5S$	Requires:	C,59.48;	H, 5.82;	N, 3.86.

(b) *N*-Hydroxy 2-({methyl-[2-(biphen-4 yloxy)ethyl]amino}sulfonyl)acetamide

[0097] In a manner similar to Example 1 (b), methyl 2-({methyl-[2-(biphen-4-yloxy)ethyl] amino} sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

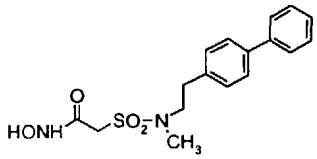
m.p. 153-155°C
^{1}H NMR (400 MHz, DMSO-d_6): d = 2.93 (s, 3H), 3.47-3.58 (m, 2H), 3.90 (s, 2H), 4.10-4.20 (m, 2H), 7.03 (d, 2H), 7.25-7.33 (m, 1H), 7.37-7.46 (m, 2H), 7.54-7.66 (m, 4H), 9.18 (s, 1H), 10.79 (s, 1H).
LRMS (APCI): 368.8 (MH^+)

Analysis:	Found:	C, 55.56;	H, 5.47;	N, 7.24.
$C_{17}H_{20}N_2O_5S$	Requires:	C, 56.03;	H, 5.53;	N, 7.69.

Example 6

N-Hydroxy 2-({methyl-[2-(biphen-4-yl)ethyl]amino) sulfonyl)acetamide

[0098]



(a) Methyl 2-({methyl-[2-(biphen-4-yl)ethyl]amino} sulfonyl)acetate

[0099] In a manner similar to Example 5 (a), methyl 2-({[2-(biphen-4-yl)ethyl]amino}-sulfonyl)acetate (Example 2 (a)) was reacted with sodium hydride and methyl *p*-toluenesulfonate to give the title compound as a colourless solid.

m.p. 72-74°C
^{1}H NMR (400 MHz, $CDCl_3$): 2.87-2.97 (m, 5H), 3.48 (t, 2H), 3.75 (s, 3H), 3.82 (s, 2H), 7.24-7.33 (m, 3H), 7.37-7.44 (m, 2H), 7.47-7.59 (m, 4H).
LRMS (Thermospray): 365.0 (MNH_4^+)
$C_{18}H_{21}NO_4S$

(b) N-Hydroxy 2-({methyl-[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetamide

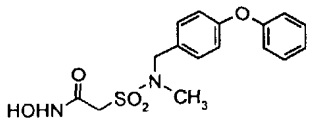
[0100] In a manner similar to Example 1 (b), methyl 2-({methyl-[2-(biphen-4-yl)ethyl] amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 166-168°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.77-2.88 (m, 5H), 3.32 (t, 2H), 3.78 (s, 2H), 7.24-7.33 (m, 3H), 7.37-7.45 (m, 2H), 7.53-7.63 (m, 4H).
LRMS (Thermospray): 365.9 (MNH_4^+)
$C_{17}H_{20}N_2O_4S$.

Example 7

N-Hydroxy 2-({methyl[4-phenoxybenzyl]amino} sulfonyl)acetamide

[0101]



(a) Methyl 2-({methyl[4-phenoxybenzyl]amino}sulfonyl)acetate

[0102] In a manner similar to Example 1 (a), N-methyl-N-(4-phenoxybenzyl)amine (Preparation 4) was reacted with methyl chlorosulfonylacetate to give the title compound as a colourless solid.

m.p. 63-64°C
^{1}H NMR (300 MHz, $CDCl_3$): 2.84 (s, 3H), 3.81 (s, 3H), 4.00 (s, 2H), 4.35 (s, 2H), 6.95-7.06 (m, 4H), 7.06-7.16 (m, 1H), 7.21-7.40 (m, 4H).
LRMS (Thermospray): 350.6 (MH^+)
$C_{17}H_{19}NO_5S$.

(b) N-Hydroxy 2-({methyl[4-phenoxybenzyl]amino}sulfonyl)acetamide

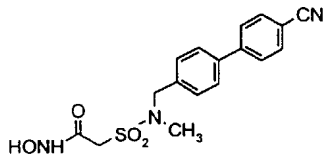
[0103] In a manner similar to Example 1(b), methyl 2-({methyl[4-phenoxybenzyl]amino}-sulfonyl) acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 154-157°C
^{1}H NMR (400 MHz, DMSO-d_6): d = 2.72 (s, 3H), 3.95 (s, 2H), 4.26 (s, 2H), 6.94-7.04 (m, 4H), 7.10-7.18 (m, 1H), 7.29-7.43 (m, 4H).
LRMS (Thermospray): 373.5 (MNa^+)

Example 8

N-Hydroxy 2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino} sulfonyl)acetamide

[0104]



(a) Methyl 2-({methyl[(4-bromophenyl)methyl]amino}suflonyl)acetate

[0105] In a manner similar to Example 1(a), *N*-methyl-*N*-(4-bromobenzyl)amine (Preparation 5) was reacted with methyl chlorosulfonylacetate to give the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): 2.83 (s, 3H), 3.82 (s, 3H), 4.03 (s, 2H), 4.33 (s, 2H), 7.25 (d, 2H), 7.50 (d, 2H).
LRMS (Thermospray): 354.3 (MNH_4^+)
$C_{11}H_{14}BrNO_4S$.

(b) Methyl-2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)acetate

[0106] To a solution of methyl 2({methyl[(4-bromophenyl)methyl]amino}sulfonyl)acetate (300 mg, 0.9 mmol) in dimethoxyethane (5 ml) was added 4-cyanophenylboronic acid (Preparation 6,150 mg, 1.0 mmol), caesium fluoride (290 mg), tri-*ortho*-tolyl phosphine (28 mg, 0.09 mmol) and bis(benzylideneacetone)palladium(0) (25 mg, 0.04 mmol) and the mixture was heated to reflux for 1 hour under an atmosphere of nitrogen. The mixture was cooled to ambient temperature, diluted with dichloromethane (30 ml) and washed with water. The organic layer was dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 2:1 as eluent) to give the titled compound as a pale yellow low melting solid (230mg).

^{1}H NMR (300 MHz, $CDCl_3$): 2.88 (s, 3H), 3.84 (s, 3H), 4.06 (s, 2H), 4.45 (s, 2H), 7.48 (d, 2H), 7.60 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H).

(c) 2-({methyl[(4'-cyanobiphen-4-yl)methy]lamino}sulfonyl)acetic acid

[0107] To a solution of methyl-2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}-sulfonyl)acetate (200 mg, 0.56 mmol) in methanol (2 ml) and tetrahydrofuran (5 ml) was added 1M aqueous sodium hydroxide solution (1.2 ml, 1.2 mmol) and the mixture was stirred at ambient temperature for 2 hours. The solution was diluted with water (10 ml), acidified to pH 2 with 2M aqueous hydrochloric acid and extracted with dichloromethane (2 x 30 ml). The combined organic layers were dried Na_2SO_4), and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid (130 mg).

m.p. 149-152°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.74 (s, 3H), 4.16 (s, 2H), 4.57 (s, 2H), 7.46 (d, 2H), 7.78 (d, 2H), 7.87 (d, 2H), 7.90 (d, 2H).

(d) *N*-Hydroxy 2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)-acetamide

[0108] *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU 263 mg, 0.72 mmol) was added to a solution of 2-({methyl[(4'-cyanobiphenyl-4-yl)methyl]amino}sulfonyl)acetic acid (185 mg, 0.48 mmol) and *N*-ethyl-*N,N*-diisopropylamine (0.08 ml, 0.48 mmol) in anhydrous dimethylformamide (3 ml) at ambient temperature under an atmosphere of nitrogen. After stirring for 20 minutes a solution of hydroxylamine hydrochloride (131 mg, 1.92 mmol) and *N*-ethyl-*N,N*-diisopropylamine (0.33 ml, 1.92 mmol) in anhydrous dimethylformamide (1 ml) was added and the solution was stirred for a further 16 hours. The mixture was partitioned between aqueous phosphate buffer (at pH 7)

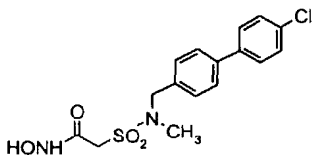
and ethyl acetate. The organic layer was washed with water, dried (MgSO4) and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia 90:10:1 as eluent) to give the title compound as a colourless solid (14 mg).

m.p. 128-130°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.73 (s, 3H), 3.97 (s, 2H), 4.33 (s, 2H), 7.44 (d, 2H), 7.74 (d, 2H), 7.85 (d, 2H), 7.91 (d, 2H).
LRMS (Thermospray): 361.0 ($M+2H^+$).

Example 9

N-Hydroxy 2-({methyl[(4'-chlorobiphen-4-yl)methyl]amino}sulfonyl)acetamide

[0109]



(a) Methyl-2-({methyl[(4'-chlorobiphen-4-yl)methyl]amino}sulfonyl)acetate

[0110] In a manner similar to Example 8 (b), methyl 2({methyl[(4'-bromophenyl-4-yl)methyl]amino}sulfonyl)acetate (Example 8 (a)) was reacted with 4-chlorophenylboronic acid to give the titled compound as a pale yellow solid.

m.p. 103-106°C
^{1}H NMR (400 MHz, $CDCl_3$): 2.87 (s, 3H), 3.83 (s, 3H), 4.04 (s, 2H), 4.43 (s, 2H), 7.38-7.46 (m, 4H), 7.48-7.59 (m, 4H).
LRMS (Thermospray): 385.2 ($M+H^+$)

(b) *N*-Hydroxy-2-({methyl[(4'-chlorobiphen-4-yl)methyl]amino}-sulfonyl)acetamide

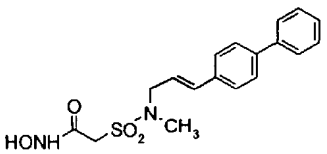
[0111] In a manner similar to Example 1 (b), methyl-2-({methyl[(4'-chlorobiphenyl-4-yl)methyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 158-161°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.72 (s, 3H), 3.95 (s, 2H), 4.32 (s, 2H), 7.40 (d, 2H), 7.49 (d, 2H), 7.66 (d, 2H), 7.69 (d, 2H), 9.22 (s, 1H), 10.83 (s, 1H).
LRMS (Thermospray): 369.8 ($M+H^+$).

Example 10

N-Hydroxy 2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl) acetamide

[0112]



(a) Methyl 2-({methyl[allyl]amino}sulfonyl)acetate

[0113] In a manner similar to Example 1 (a), *N*-methyl-*N*-allylamine was reacted with methyl chlorosulfonylacetate to give the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 2.89 (s, 3H), 3.81 (s, 3H), 3.81 (d, 2H), 3.97 (s, 2H), 5.03-5.15 (m, 2H), 5.74-5.88 (m, 1H).

(b) Methyl- 2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate

[0114] To a solution of methyl 2-({methyl[allyl]amino}sulfonyl)acetate (300 mg, 1.4 mmol) and 4-bromobiphenyl (370 mg, 1.54 mmol) in acetonitrile (4 ml) was added triethylamine (0.3 ml, 2.1 mmol), palladium(II) acetate (17 mg, 0.07 mmol) and tri-*ortho*-tolyl phosphine (52 mg, 0.14 mmol) and the solution was heated to reflux under an atmosphere of nitrogen for 3 hours. The mixture was cooled to ambient temperature, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (dichloromethane as eluent) to give the title compound as a pale yellow solid (300 mg).

m.p. 104-107°C
^{1}H NMR (300 MHz, $CDCl_3$): 2.97 (s, 3H), 3.86 (s, 3H), 4.00-4.13 (m, 4H), 6.24 (dt, 1H), 6.66 (d, 1H), 7.33-7.40 (m, 1H), 7.41-7.54 (m, 4N), 7.58-7.71 (m, 4H).
LRMS (Thermospray): 377.2 (MNH_4^+).

(c) *N*-Hydroxy-2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)-acetamide

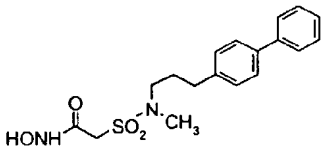
[0115] In a manner similar to Example 1 (b), methyl 2-({methyl[3-(1,1'-biphenyl-4-yl)*trans*-prop-2-enyl]amino} sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 153-155°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.82 (s, 3H), 3.88-3.97 (m, 4H), 6.34 (dt, 1H), 6.66 (d, 1H), 7.36 (d, 1H), 7.43 (d, 1H), 7.46 (d, 1H), 7.56 (d, 2H), 7.64 (d, 2H), 7.67 (d, 2H), 9.20 (s, 1H), 10.81 (s, 1H).
LRMS (Thermospray): 362.2 ($M+2H^+$).

Example 11

N-Hydroxy 2-({methyl[3-(biphen-4-yl)-prop-1-yl]amino}sulfonyl)acetamide

[0116]



(a) Methyl- 2-({methyl[3-(biphen-4-yl)-propyl]amino}sulfonyl)acetate

[0117] To a solution of methyl- 2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate (Example 10 (b), 200 mg, 0.56 mmol) and ammonium formate (175 mg, 2.8 mmol) in methanol (5 ml) was added 20% palladium hydroxide on carbon (50 mg) and the mixture was heated to reflux for 4 hours. The mixture was cooled to ambient temperature, filtered through arbocel and the filtrate was concentrated under reduced pressure to give the title compound as a pale yellow solid (193 mg).

m.p. 66-70°C

^{1}H NMR (300 MHz, $CDCl_3$): 1.89-2.04 (m, 2H), 2.72 (t, 2H), 2.95 (s, 3H), 3.30 (t, 2H), 3.80 (s, 3H), 3.97 (s, 2H), 7.23-7.38 (m, 3H), 7.40-7.47 (m, 2H), 7.54 (d, 2H), 7.59 (d, 2H).
LRMS (Thermospray): 379.2 (MNH_4^+).

(b) *N*-Hydroxy 2-({methyl[3-(biphen-4-yl)-propyl]amino}sulfonyl)acetamide

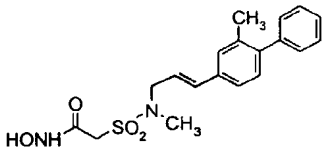
[0118] In a manner similar to Example 1 (b), methyl-2-({methyl[3-(biphen-4-yl)-propyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 137-140°C
^{1}H NMR (300 MHz, DMSO-d_6): 1.75-1.93 (m, 2H), 2.61 (t, 2H), 2.82 (s, 3H), 3.18 (t, 2H), 3.83 (s, 2H), 7.25-7.36 (m, 3H), 7.40-7.50 (m, 2H), 7.57 (d, 2H), 7.64 (d, 2H), 9.05-9.28 (br s, 1H).
LRMS (Thermospray): 380.2 (MNH_4^+).

Example 12

N-Hydroxy 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}-sulfonyl)acetamide

[0117]



(a) Methyl 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate

[0120] In a manner similar to Example 10 (b), methyl 2-({methyl[allyl]amino}sulfonyl)acetate (Example 10 (a)) was reacted with 4-bromo-2-methylbiphenyl (Preparation 7) to give the title compound as a pale yellow low melting solid.

^{1}H NMR (400 MHz, $CDCl_3$): 2.29 (s, 3H), 2.97 (s, 3H), 3.93 (s, 3H), 4.00-4.07 (m, 4H), 6.23 (dt, 1H), 6.62 (d, 1H), 7.18-7.47 (m, 8H).
LPMS (Thermospray): 391.9 (MNH_4^+).

(b) *N*-Hydroxy 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}-sulfonyl)acetamide

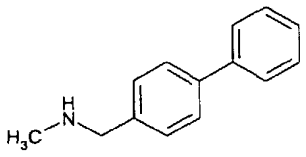
[0121] In a manner similar to Example 1 (b), methyl 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the titled compound as a colourless solid.

m.p. 146-149°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.23 (s, 3H), 2.81 (s, 3H), 3.82-4.02 (m, 4H), 6.33 (dt, 1H), 6.62 (d, 1H), 7.17 (d, 1H), 7.25-7.49 (m, 7H), 9.21 (s, 1H), 10.82 (s, 1H).
LPMS (Thermospray): 376.1 ($M+2H^+$)

Preparation 1

N-Methyl-*N*-[(biphen-4-yl)methyl]amine

[0122]



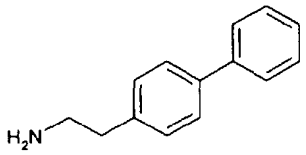
[0123] To a solution of biphenyl-4-carboxaldehyde (4.6 g, 25 mmol) in ethanol (50 ml) was added methylamine (3.0 ml of 33% solution in ethanol, 25 mmol) and acetic acid (1.4 ml, 25 mmol), and the mixture was stirred under an atmosphere of nitrogen. After 20 minutes sodium tri(acetoxy)borohydride (10.5 g, 50 mmol) was added and stirring was continued for 16 hours. The mixture was diluted with 2M aqueous hydrochloric acid (200 ml) and washed with ethyl acetate (3 x 100 ml). The aqueous layer was basified to pH 12 with concentrated aqueous ammonia solution and extracted with dichloromethane (4 x 100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil (2.5 g).

^{1}H NMR (300 MHz, $CDCl_3$):1.38 (br s, 1H), 2.50 (s, 3H), 3.80 (s, 2H), 7.30-7.48 (m, 5H), 7.52-7.64 (m, 4H).

Preparation 2

2-(Biphen-4-yl)ethylamine

[0124]

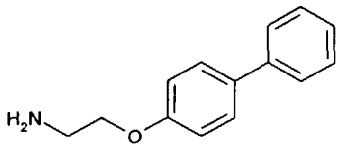


[0125] This was prepared according to the method described by W. W. Zacac Jr, J. F. Siuda, M. J. Nolan and T. M. Santususso, in *J. Org. Chem.* 1971, *36*, 3539.

Preparation 3

2-(Biphen-4-yloxy)ethylamine

[0126]



(a) 2-([Biphen-4-yloxy]ethyl)isoindoline-1,3-dione

[0127] Potassium phthalimide (1.2 g, 6.5 mmol) was added to a solution of 4-(2-chloroethoxy)-1,1'-biphenyl (1.0 g, 5.4 mmol) in anhydrous dimethylformamide (3 ml) and anhydrous dimethylsulfoxide (3 ml) and the mixture was heated to 70°C under an atmosphere of nitrogen for 5 hours. The mixture was cooled to ambient temperature and partitioned between water and dichloromethane. The organic layer was washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound as a colourless solid (1.51 g).

^{1}H NMR (300 MHz, $CDCl_3$): 4.13 (t, 2H), 4.26 (t, 2H), 6.96 (d, 2H), 7.23-7.34 (m, 1H), 7.34-7.44 (m, 2H), 7.44-7.58 (m, 4H), 7.67-7.80 (m, 2H), 7.83-7.93 (m, 2H).
LPMS (Thermospray): 343.3 (M^+).

(b) 2-(Biphen-4-yloxy)ethylamine

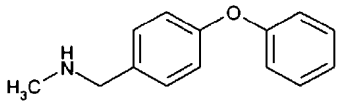
[0128] To a solution of 2-([biphen-4-yloxy]ethyl)isoindoline-1,3-dione (1.5 g, 4.4 mmol) in dichloromethane (30 ml) was added methylamine (33% solution in ethanol, 50 ml) and the solution was heated to reflux under an atmosphere of nitrogen for 2 hours. The mixture was cooled to ambient temperature, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonium solution 95:5:0 to 94:5:1 as eluent) to give the title compound as a colourless solid (505 mg).

^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (s, 2H), 3.05-3.19 (m, 2H), 3.98-4.12 (m, 2H), 6.98 (d, 2H), 7.22-7.66 (m, 7H).
LRMS (Thermospray): 214.0 (MH^+).

Preparation 4

N-Methyl-*N*(4-phenoxybenzyl)amine

[0127]



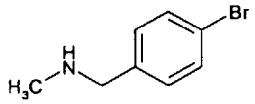
[0130] To a solution of 4-phenoxybenzaldehyde (4.4 ml, 25 mmol) in ethanol (50 ml) was added methylamine (3.0 ml of 33% solution in ethanol, 25 mmol) and acetic acid (1.4 ml, 25 mmol), and the mixture was stirred under an atmosphere of nitrogen. After 20 minutes sodium tri(acetoxy)borohydride (10.5 g, 50 mmol) was added and stirring was continued for 16 hours. The mixture was diluted with 2M aqueous hydrochloric acid (200 ml) and washed with diethyl ether (2 x 100 ml). The aqueous layer was basified to pH 12 with concentrated aqueous ammonia solution and extracted with dichloromethane (4 x 100ml). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 95:5:0 to 94:5:1) to give the titled compound as a colourless oil (3.3 g).

^{1}H NMR (300 MHz, $CDCl_3$): 2.33 (s, 1H), 2.47 (s, 3H), 3.73 (s, 2H), 6.93-7.02 (m, 4H), 7.02-7.13 (m, 1H), 7.23-7.37 (m, 4H).

Preparation 5

N-Methyl-*N*-(4-bromobenzyl)amine

[0131]

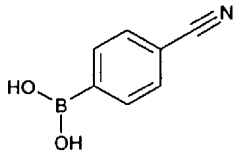


[0132] This was prepared according to the method of G. M. Singer et al, described in *J. Med. Chem.* 1986, *29,* 40.

Preparation 6

4-Cyano-phenylboronic acid

[0133]

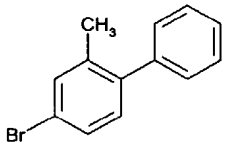


[0134] This was prepared according to the method of G. J. Pernia et al, described in *J. Am. Chem. Soc.* 1996, *118,* 10220.

Preparation 7

4-Bromo-2-methylbiphenyl

[0135]



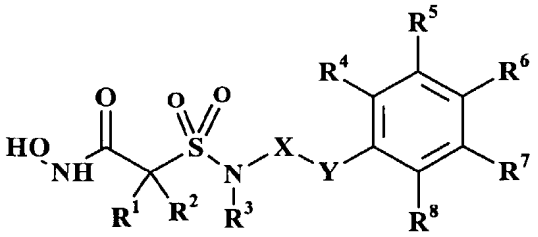
[0136] This was prepared according to the method of M. Gomberg et al, described in *J. Am Chem. Soc.* 1926, *48,* 1372.

Biological Data

[0137] The substances of Examples 1-12 had MMP-3 IC_{50} values of 1.5μM or less. The substances of Examples 1-12 had MMP-2 IC_{50} values of 6.3μM or less. Certain of the substances of the Examples had MMP-13 IC_{50} values of 0.05μM or less.

Claims

1. A compound of formula (I):



(I)

and a pharmaceutically- and/or veterinarily-acceptable salt thereof, and a solvate of such compound and salt, wherein

R^1 and R^2 are each independently H,
C_{2-6} alkenyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl), aryloxy(C_{1-6} alkyl), heteroaryloxy-(C_{1-6} alkyl),
C_{1-6} alkyl optionally substituted by NH_2, C_{2-6} acylamino, OH, or by CO_2H
or R^1 and R^2 can be taken together with the carbon atom to which they are attached, to form a 4- to 8-membered saturated carbocyclic or heterocyclic ring, which heterocyclic ring has 1 or 2 hetero-groups selected from O, $S(O)_n$ or NR^9 in the ring,
R^3 is H, C_{1-6} alkyl or (C_{1-6} alkoxy)C_{1-6} alkyl,
R^4, R^5, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^6 is H, aryl, heteroaryl, aryloxy or heteroaryloxy, C_{1-6}alkyl, C_{1-6} alkoxy, CN or halogen,
R^9 is H or C_{1-6} alkyl,
n is 0,1 or 2,
X is C_{1-6} alkylene or C_{2-6} alkenylene,
Y is a direct link, CH=CH or O,

wherein "aryl" is phenyl optionally fused with another ring selected from furan, dioxolan, and pyran, which group is optionally mono- or disubstituted by substituents independently seleceted from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy), and wherein "heteroaryl" is a 5- or 6-membered aromatic heterocycle with one or two heteroatoms in the ring, which heteroatoms are independently selected from O, N and S, which heteroaryl is optionally mono- or disubstituted by substituents independently selected from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy).

2. A substance according to claim 1 wherein R^1 is H.

3. A substance according to any preceding claim wherein R^2 is H.

4. A substance according to any preceding claim wherein R^3 is H or C_{1-6} alkyl.

5. A substance according to any preceding claim wherein R^4 is H.

6. A substance according to any preceding claim wherein R^5 is H or C_{1-6} alkyl.

7. A substance according to any preceding claim wherein R^6 is H, aryl[1] or aryl[1]oxy wherein "aryl" is phenyl optionally mono- or disubstituted by substituents selected from halogen and CN.

8. A substance according to any preceding claim wherein R^7 is H.

9. A substance according to any preceding claim wherein R^8 is H.

10. A substance according to any preceding claim wherein X is CH_2, $(CN_2)_2$, $(CN_2)_3$, or is $CH_2CH=CH$ wherein the terminal methinyl carbon of this group is linked to the Y moiety.

11. A substance according to any preceding claim wherein R^3 is H or CH_3.

12. A substance according to any preceding claim wherein $R^5$is H or CH_3.

13. A substance according to any preceding claim wherein R^6 is H, $aryl^2$ or $aryl^2$oxy wherein "$aryl^2$" is phenyl optionally 4-substituted by substituents selected from Cl and CN.

14. A substance according to any preceding claim wherein R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl.

15. A substance according to any preceding claim wherein at least two of the groups R^4, R^5, R^7 and R^8 are all H.

16. A substance according to any preceding claim wherein R^4, R^7 and R^8 are all H and R^5 is CH_3.

17. A substance according to any preceding claim wherein R^1, R^2, R^4, R^7 and R^8 are all H,

R^3 is H or CH_3,
$R^5$is H or CH_3,
R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl,
X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or is $CH_2CH=CH$ wherein the terminal methine carbon of this group is linked to the Y moiety,
and the salts and solvates thereof.

18. A substance according to claim 1 as described herein in the Examples and the salts and solvates thereof.

19. A pharmaceutical composition comprising a substance according to any one of claims 1 to 18, together with a pharmaceutically acceptable diluent or carrier.

20. A veterinary composition comprising a substance according to any one of claims 1 to 18, together with a veterinarally acceptable diluent or carrier.

21. A substance according to any one of claims 1 to 18 for use as a medicament.

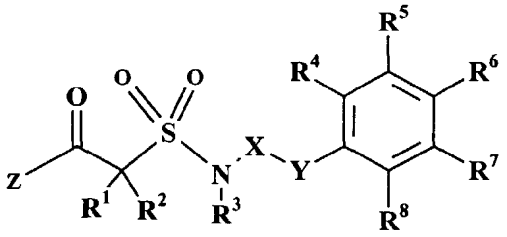
22. The use of a substance according to any one of claims 1 to 18 in the manufacture of a medicament for the treatment of a condition mediated by one or more MMPs.

23. The use of a substance according to any one of claims 1 to 18 in the manufacture of a medicament for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wounds, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

24. A method of treating a condition mediated by one or more MMPs, in an animal such as a mammal (including a human being), which comprises administering to said animal an effective amount of a substance according to any one of claims 1 to 18.

25. A method of treating atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wounds, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells, in an animal such as a mammal (including a human being), which comprises administering to said animal an effective amount of a substance according to any one of claims 1 to 18.

26. A compound of formula (II):



(II)

where Z is chloro, bromo, iodo, C_{1-3} alkyloxy or HO, and X, Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in claim 1, or a salt thereof.

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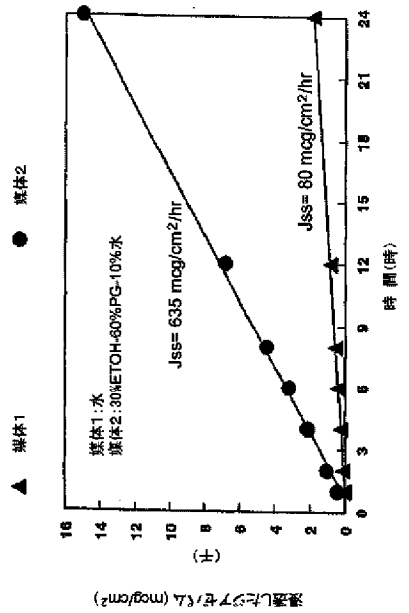
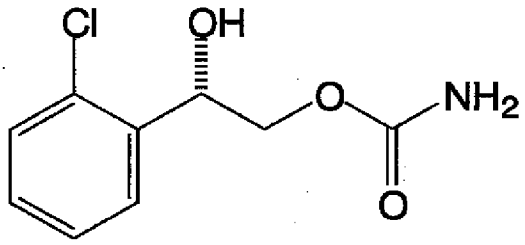
(54)【発明の名称】　経鼻抗痙攣組成物及び調節方法

(57)【要約】
媒体によって調節して、ヒト及び動物の粘膜に抗痙攣剤を投与する新規な方法を開示する。媒体系は、胆汁塩又はレシチンのような生物学的活性剤と共に、脂肪族アルコール（１０－８０％）、又はグリコール（１０－８０％）、及びそれらの組み合わせを含む、水性の薬学的担体である。薬学的組成物は、１回又は複数回投与することにより、粘膜を介した薬剤の浸透及び吸収の速度及び量を調節及び促進するための手段を提供する。薬学的組成物の経鼻投与は、静脈内投与と同じ位素早く、抗痙攣剤の高い血漿濃度をもたらす。そのような組成物は、発作重積状態及び他の発熱によって引き起こされる発作の救急及び／又は緊急治療における、患者の迅速かつ適時の薬物治療に特に適している。

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ウサギにおける本発明の調製物のＩＶ及びＩＮ投与後のジアゼパムの生物学的利用能及び薬学動力学パラメーター

経路/製剤	投薬(mg/kg)	C_{max} (ng/ml)	T_{max}(分)	$AUC_{(0-120分)}$ (ng×分/ml)	F(%)
IV 処方 1[a]	1回 (1mg/kg×1)	398.8 (63.0)[d]	2.0	17582 (407)[d]	100.0 (n=3)
IN 処方 2[b]	1回 (1mg/kg×1)	273.6 (62.2)[d]	5.0	10383 (692)[d]	59.1 (n=3)
IN 処方 3[c]	1回 (1mg/kg×1)	273.7 (26.4)[d]	2.0	13300 (972)[d]	75.7 (n=4)
IN 処方 3[c]	2回 (1mg/kg×2)[f]	327.1 (29.7)[d] 556.9 (130.5)[d]	2.0 10.0	26787 (4859)[d]	76.2[e] (n=3)
IN 処方 4[g]	1回 (1mg/kg×1)	73.3 (11.9)[d]	30.0	7497 (1445)[d]	42.6 (n=3)

[a]ＩＶ処方１：０．５％ジアゼパム注射、ＵＳＰ、エルキンスーシン社(Elkins-Sinn,Inc.)（ＰＧ／ＥＴＯＨ／ベンジルアルコール／ベンゾエートナトリウム塩／安息香酸／注射用の水）

[b]ＩＮ処方２：２％のジアゼパム溶液を含む６０％ＰＧ、３０％ＥＴＯＨ、及び１０％水

[c]ＩＮ処方３：２％のジアゼパム溶液を含む１％ＳＧＣ、６０％ＰＧ、３０％ＥＴＯＨ、及び１０％水

[d]標準偏差

[e]以下の式を用いて決定された標準化したデータ：

$$F = \{AUC_{IN,1\ mg\ x\ 2} / 2 \times AUC_{IV,\ 1\ mg\ x\ 1)} \times 100\}$$

[f]適用時間：$t_{ゼロ}$：最初の経鼻投薬

$t_{5分}$：２回目の経鼻投薬

[g]ＩＮ処方４：２％のジアゼパム溶液を含むクレモフォア(Cremophor)ＥＬ

ウサギにおける本発明の調製物のＩＶ及びＩＮ投与後のジアゼパムの薬学動力学パラメーターへの媒体のＥＴＯＨ／ＰＧ容量比の効果

経路/製剤	投薬(mg/kg)	C_{max} (ng/ml)	T_{max}(分)	$AUC_{(0-120分)}$ (ng×分/ml)	F(%)
IV 処方１[a]	１回 (1mg/kg×1)	398.8 (63.0)[e]	2.0	17582 (407)[e]	100.0 (n=3)
IN 処方Ａ[b]	１回 (1mg/kg×1)	313.2 (17.3)[e]	2.0	13592 (692)[e]	77.3 (n=3)
IN 処方Ｂ[c]	１回 (1mg/kg×1)	273.7 (26.4)[e]	2.0	13300 (972)[e]	75.7 (n=4)
IN 処方Ｃ[d]	１回 (1mg/kg×１)	246.3 (32.2)[e]	2.0	12860 (827)[e]	73.1 (n=3)

[a]ＩＶ処方１：０．５％ジアゼパム注射、ＵＳＰ、エルキンスーシン社(Elkins-Sinn,Inc.)（ＰＧ／ＥＴＯＨ／ベンジルアルコール／ベンゾエートナトリウム塩／安息香酸／注射用の水）

[b]ＩＮ処方Ａ：２％のジアゼパム溶液を含む１％ＳＧＣ、３０％ＰＧ、６０％ＥＴＯＨ、及び１０％水

[c]ＩＮ処方Ｂ：２％のジアゼパム溶液を含む１％ＳＧＣ、６０％ＰＧ、３０％ＥＴＯＨ、及び１０％水

[d]ＩＮ処方Ｃ：２％のジアゼパム溶液を含む１％ＳＧＣ、７０％ＰＧ、２０％ＥＴＯＨ、及び１０％水

[e]標準偏差

ウサギへの調製物のＩＶ及びＩＮ投与後のクロナゼパムの生物学的利用能及び薬学動力学パラメーター

経路/製剤	投薬(mg/kg)	C_{max} (ng/ml)	T_{max}(分)	$AUC_{(0-120\ 分)}$ (ng×分/ml)	F(%)
IV 処方[a]	１回 (0.2mg/kg ×1)	104.8	2.0	7437.7	100.0 (n=2)
IN 処方[b]	１回 (0.2mg/kg ×1)	32.9 (5.9)[c]	2.0	3356.4 (544.8)[c]	45.1 (n=3)
IN 処方[b]	２回[f] (0.2mg/kg ×2)	49.5 (5.3)[c]	10.0	4896.8 (836.6)[c]	32.9[d] (n=4)
IN 処方[b]	３回[f] (0.2mg/kg ×3)	80.2 (21.3)[c]	15.0	7766.1 (2077.9)[c]	34.8[e] (n=3)

[a]ＩＶ処方：０．１５%クロナゼパム溶液を含む４０%ＰＧ、３０%ＥＴＯＨ、及び３０%水

[b]ＩＮ処方：０．４２%のクロナゼパム溶液を含む１%ＳＧＣ、６０%ＰＧ、３０%ＥＴＯＨ、及び１０%水

[c]標準偏差

[f]以下の式を用いて算出された標準化したデータ：

$$F = \{AUC_{IN,0.2\ mg\ x\ 2} / 2 \times AUC_{IV,\ 0.2\ mg\ x\ 1}\} \times 100\}$$

[l]以下の式を用いて算出された標準化したデータ：

$$F = \{AUC_{IN,0.2\ mg\ x\ 3} / 3 \times AUC_{IV,\ 0.2\ mg\ x\ 1}\} \times 100\}$$

[f]適用時間：$t_{ゼロ}$：最初の経鼻投薬
$t_{5分}$：２回目の経鼻投薬
$t_{10分}$：３回目の経鼻投薬

２つの投与強度での、１回のＩＶおよびＩＮ投与後の（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノールの薬学動力学パラメーター

経路/製剤	投薬(mg/kg)	最大濃度 (ng/ml)	T_{max}(分)	$AUC_{(0-240\ 分)}$ (ng×分/ml)	F(%)
IV 処方[a]	5.0	6267.7 (408.0)[d]	2.0	473176 (56105)[d]	100.0 (n=4)
IN 処方１[b]	5.0	2404.9 (130.0)[d]	30.0	373991 (5077)[d]	79.1 (n=3)
IV 処方[a]	2.5	4179.9	2.0	221291	100.0 (n=2)
IN 処方２[c]	2.5	1407.2	5.0	160269	72.4 (n=2)

[a]ＩＶ処方：０．１５％（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノール溶液を含む４０％ＰＥＧ４００及び６０％水

[b]ＩＮ処方１：　１０％の（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノール溶液を含む１％ＳＧＣ、６０％ＰＧ、３０％ＥＴＯＨ、及び１０％水

[b]ＩＮ処方２：　５％の（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノール溶液を含む１％ＳＧＣ、６０％ＰＧ、３０％ＥＴＯＨ、及び１０％水

１回及び３回の投与計画における調製物のＩＶ及びＩＮ投与後の（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノールの生物学的利用能及び薬学動力学パラメーター

経路/製剤	投薬(mg/kg)	最大濃度 (ng/ml)	T_{max}(分)	$AUC_{(0-120\ 分)}$ (ng×分/ml)	F(%)
IV 処方[a]	１回 (5mg/kg×1)	6267.7 (408.0)[c]	2.0	473176 (56105)[c]	100.0 (n=4)
IN 処方[b]	１回 (5mg/kg×1)	2404.9. (130.0)[c]	30.0	373991 (5077)[c]	79.1 (n=3)
IN 処方[b]	２回[e] (5mg/kg×2)	4332.3 (979.3)[c]	30.0	700475 (114195)[c]	74.1[d] (n=3)

[a]ＩＶ処方：１．５％（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノール溶液を含む４０％ＰＥＧ及び６０％水

[b]ＩＮ処方：１０％の（Ｓ）－２－カルバモイロキシル－１－ｏ－クロロフェニルエタノール溶液を含む１％ＳＧＣ、６０％ＰＧ、３０％ＥＴＯＨ、及び１０％水

[c]標準偏差

[d]以下の式を用いて決定された標準化したデータ：

$$F = \{AUC_{IN,5\ mg\ x\ 2} / 2 \times AUC_{IV,\ 5\ mg\ x\ 1)} \times 100\}$$

[e]適用時間：$t_{ゼロ}$：最初の経鼻投薬

$t_{5分}$：２回目の経鼻投薬

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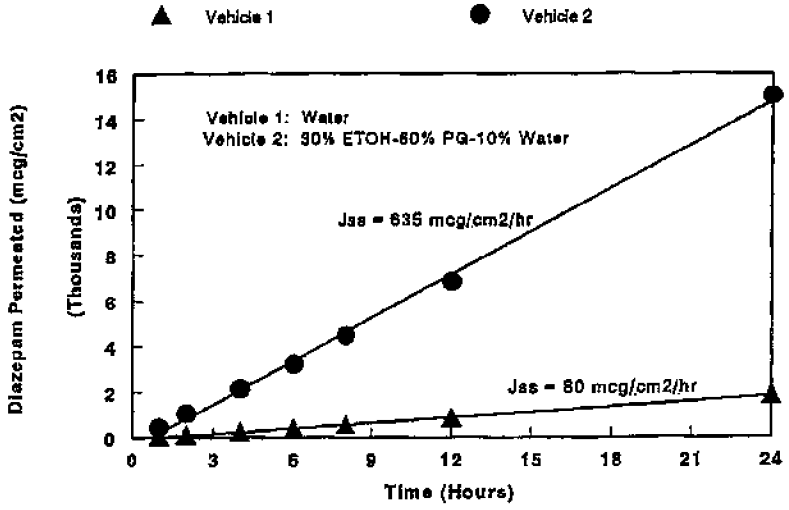
(54) Title: TRANSNASAL ANTICONVULSIVE COMPOSITIONS AND MODULATED PROCESS



(57) Abstract: A novel method of vehicle modulated administration of an anticonvulsive agent to the mucous membranes of humans and animals is disclosed. The vehicle system is an aqueous pharmaceutical carrier comprising an aliphatic alcohol (10-80 %) or a glycol (10-80 %), and their combinations with a biological surfactant such as a bile salt or a lecithin. The pharmaceutical composition provides a means to control and promote the rate and extent of transmucosal permeation and absorption of the medicaments via a single and multiple administration. Nasal administration of the pharmaceutical preparation produces a high plasma concentration of the anticonvulsant nearly as fast as intravenous administration. Such compositions are particularly suitable for a prompt and timely medication of patients in the acute and/or emergency treatment of status epilepticus and other fever-induced seizures.

WO 01/06987 A2

TRANSNASAL ANTICONVULSIVE COMPOSITIONS AND MODULATED PROCESS

FIELD OF THE INVENTION

The present invention is directed to pharmaceutical compositions for transmucosal delivery of biologically active agents. More particularly, this invention relates to a novel method for controlling and promoting the rate and extent of transmucosal permeation and absorption of an anticonvulsive agent by coadministration of the medicament with a pharmaceutically acceptable co-solvent system comprising an aliphatic alcohol, a glycol, and water, and their combinations with a biological surfactant such as a bile salt or a lecithin. Even more particularly, this invention relates to the pharmaceutical compositions to provide a patient-acceptable transnasal anticonvulsive delivery system, which may be useful for the emergency management of status epilepticus and fever seizures in a prompt and convenient manner of administration.

BACKGROUND OF THE INVENTION

Status epilepticus is a neurological emergency in which mortality ranges from 3 – 35%. The major goal of treatment is rapid management of pathological seizure activity; the longer that the episode of status epilepticus is untreated, the more difficult it is to control and the greater the risk of permanent brain damage. Thus, critical to the management of the patient is a clear plan, involving prompt treatment with effective drugs in adequate doses having a proper pharmaceutical formulation as well as attention to hypoventilation and hypotension.

Currently several drug regimens have been proven to be applicable in treating status epilepticus. Diazepam and lorazepam are the most widely used benzodiazepines for this purpose. Intravenous administration of anticonvulsants is the most rapid way to suppress epileptic convulsions. However, other routes of administration may be highly desirable when intravenous administration is inconvenient and delaying, for instance, because of technical difficulties such as requirements for sterile equipment and skilled

personnel, and because of the possible development of thrombophlebitis. In addition, intravenous medication is often associated with hypotension, cardiac dysrhythmia or central nervous system depression. In this regard Moolenaar [Moolenaar et al., *Int. J. Pharm.*, 5: 127-137 (1986)] attempted to administer diazepam in humans via several other routes such as intramuscular injection, oral tablet and rectal solution. Only the rectal administration was found to provide a fairly rapid absorption and thus, it might be looked upon as an alternative route to IV injection. However, the rectal route is a very inconvenient way of drug administration particularly in emergency treatment. In U.S. Patent No. 4,863,720 of Burghardt, a sublingual sprayable pharmaceutical preparation is disclosed, in which the active drug can be a benzodiazepine, optimally comprising polyethylene glycol (PEG) and requiring ethanol, di- and/or triglyceride of fatty acids and a pharmaceutically acceptable propellant gas.

More recently, it appears that the mucosal membrane of the nose offers a practical route of administration for therapeutic effect of many medicinal substances. Intranasal administration has the advantages that drugs may be administered readily and simply to achieve a systemic or localized effect, as required. However, the major problem associated with intranasal drug administration is the fact that most drug molecules diffuse poorly and slowly through the nasal mucosal membrane and thus the desired levels of the therapeutic agent cannot be achieved by means of simple transnasal administration. An additional constraint concerning nasal administration is that a small administration volume is needed; it is not generally possible to administer more than approximately 150 µl per nostril; above this, the formulation will be drained out into the pharynx and swallowed. Therefore, a great need exists for solvent vehicles, in which the solubility of the drug is high and which, on the other hand, are non-irritating to the nasal mucosa. The intranasal absorption of drugs can be increased by coadministering a chemical adjuvant or permeation enhancers. For example, Lau and Slattery [Lau et al., *Int. J. Pharm.*, 54: 171-174 (1989)] attempted to administer a benzodiazepine such as diazepam and lorazepam by dissolving these medicaments in a variety of solvents; triacetin, dimethylsulfoxide, PEG 400, Cremophor EL, Lipal-9-LA, isopropyl adipate and Azone. While many of the solvents dissolved diazepam and lorazepam in the desired concentrations, they were too

irritable to be used when administered to the nose. Cremophor EL was found to be the least irritating for nasal mucosal tissue, but the nasal absorption in the use of this vehicle in humans was rather slow ($T_{max} \cong 1.4$ hours) and the peak concentration was low relative to that observed after IV administration. In U.S. Patent No. 4,950,664 Rugby described the nasal administration of a benzodiazepine hypnotic in a pharmaceutically acceptable nasal carrier. The carrier may be an aqueous saline solution, an alcohol, a glycol, a glycol ether or mixtures thereof. The results of pharmacokinetic studies in dogs showed that the time to maximum plasma concentration for triazolam was achieved at 18 minutes after the nasal administration, while an effective treatment within 5 minutes is considered to be an attractive goal. Bechgaard and Hjortkjer [Bechgaard et al., *J. Pharm. Pharmacol.*, 49: 747-750 (1997)] described the use of pure organic solvents such as glycofurol and tetraethyleneglycol, and their combinations as carriers for nasal delivery of diazepam. The absolute bioavailability, measured during the first 30 minutes after the nasal administration, was 49-62% for the most promising carrier systems examined. In PCT WO 95/31217, Dumex described the use of a pharmaceutical emulsion preparation based on tocopherol and its derivatives for intranasal administration of biologically active compounds including benzodiazepines.

SUMMARY OF INVENTION

The present invention is a novel method of vehicle modulated administration of an anticonvulsive agent to the mucous membranes of humans and animals. The vehicle system is an aqueous pharmaceutical carrier comprising an aliphatic alcohol or a glycol and their combinations with a biological surfactant such as a bile salt or a lecithin.

An objective of the present invention is to provide a pharmaceutically acceptable carrier system which is capable of enhancing the transmucosal permeation and absorption of an anticonvulsive agent. The ingredients used in the pharmaceutical composition are preferably those of GRAS materials (generally recognized as safe), so there are no major toxicity issues of concern. Another objective of the present invention is to provide a method of controlling the transmucosal delivery of an anticonvulsant at an appropriately

adjusted rate so as to achieve an optimum therapeutic effect, while avoiding or reducing adverse side effects. Such compositions are particularly suitable for intranasal administration of the medicaments in the acute treatment of status epilepticus and fever seizures.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the effect of a vehicle on the *in vitro* transnasal permeation of diazepam preparations of the invention.

Fig. 2 is a graph showing the effect of drug concentration level on the *in vitro* transnasal permeation of diazepam from a vehicle of the invention.

Fig. 3 is a graph showing the influence of sodium glycocholate (SGC) on the *in vitro* transnasal permeation of diazepam from a vehicle of the invention.

Fig. 4 is a graph showing the mean plasma concentration-time profiles of diazepam after intravenous (IV) administration and intranasal administration of a preparation in accordance with the invention (a single dose application).

Fig. 5 is a graph showing the mean plasma concentration-time profiles of diazepam after intravenous and intranasal administration of a preparation in accordance with the invention (a multiple dose application).

Fig. 6 is graph showing the mean plasma concentration-time profiles of diazepam after intranasal administration of a preparation as a function of propylene glycol/ethanol volume ratio in the preparation according to the invention.

Fig. 7 is a graph showing the mean plasma concentration profiles of clonazepam after intravenous administration and intranasal administration of a preparation in accordance with the invention (a single and multiple dose application).

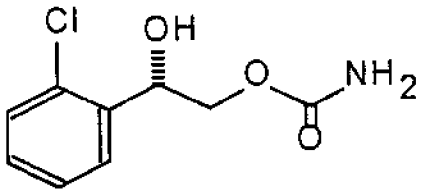
Fig. 8 is a graph showing the mean plasma concentration-time profiles of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol after intravenous administration and intranasal administration of a preparation according to the invention as a function of dose strength.

Fig. 9 is a graph showing the mean plasma concentration-time profiles of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol after intravenous administration and intranasal

administration of a preparation according to the invention (a single and multiple dose application).

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, a certain aqueous co-solvent system comprising one aliphatic alcohol, one glycol and a biological surfactant provides a rate-controlled and enhanced transnasal delivery of an anticonvulsive agent. The alcohol of the present invention is selected from C_1 to C_5 aliphatic alcohols; a glycol is selected from propylene glycol (PG), polyethylene glycol (PEG) 200, PEG 300 and PEG 400, and PEG 600; and a biological surfactant is selected from bile salts such as sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, and sodium ursodeoxycholate or a lecithin such as lysophosphatidylcholines, phosphatidylcholines, phosphatidylserines, phosphatidylinositols, phosphatidylethanolamines, and phosphatidylglycerols. The above-described compositions can be used for medicinal preparations comprising anticonvulsive agents applicable to the mucosal membranes of humans and animals. More specifically, these compositions are ones which comprise a benzodiazepine such as diazepam, clonazepam, and lorazepam, and a monocarbamate based new anticonvulsive compound, (S)-2-carbamoyloxyl-1-o-chlorophenylethanol represented by the following formula:



adapted for intranasal administration in a solution, suspension, gel or other useful nasal formulation. These nasal compositions may be employed for any of the known therapeutic purposes for which such anticonvulsants are known including phenytoins

(phenytoin, mephenytoin and ethotoin), barbiturates (phenobarbital, mephobarbital, and primidone), iminostilbenes (carbamazepine), succinimides (ethosuximide), valproic acid, oxazolidinediones (trimethadione) and other antiseizure agents (gabapentin, lamotrigine, acetazolamide, felbamate, and γ-vinyl GABA). The utilization of an intranasal formulation of the anticonvulsant greatly facilitates administration. As compared with parenteral administration, for example, a simple sprayer, dropper or nebulizer will suffice for prompt and convenient delivery of the medicaments, in particular, for the emergency treatment of acute convulsive attack phenomena of epilepsy. From a clinical point of view, intranasal administration often provides an improved duration of anticonvulsive effect. By the present invention, the therapeutic effect, in terms of onset, intensity, and duration, can be more efficiently and accurately controlled by varying the proportion of aliphatic alcohol and glycol in the vehicle and by a single-dose and/or multiple-dose administration of the preparation of the invention. Although this invention has been described with respect to an anticonvulsant as a model compound, it is understood that this invention is also applicable to the other biologically active agents that are applicable to the mucosal membranes of humans and animals.

The invention is further illustrated by the following examples, which are illustrative of a specific mode of practicing the invention and are not intended as limiting the scope of the appended claims.

Example 1

In Vitro Nasal Membrane Permeation Studies

The nasal mucous membrane used in these *in vitro* experiments was obtained from New Zealand White rabbits (2.5 – 3.0 kg). Rabbits were sacrificed by IV injection of phenobarbital. The nasal septum was carefully removed from a bone block using surgical scissors and a bone-cutting saw. Two pieces of nasal mucous membranes were then carefully stripped from the nasal septum without touching the center of the membrane surface and rinsed with normal saline solution. The mucosal membrane was mounted between two half-cells of a glass diffusion cell apparatus. The exposed area of

the nasal membrane was approximately 0.64 cm^2. A test solution or suspension (3.5 ml) was introduced into the mucosal side of the membrane in the donor compartment while 3.5 ml of 10% ethanol, 40% propylene glycol, and 50% pH 7.4 isotonic phosphate buffer solution was added to the receptor compartment. The entire diffusion system was maintained at 37°C throughout the experiment. At predetermined time intervals, 100 µl of the receptor solution was withdrawn for the assay and refilled with the same volume of fresh receptor medium to keep the volume constant. The steady-state flux value was determined from the slope of the straight line attained from the plot of the cumulative amount of drug permeated as a function of time. Each experiment was carried out in at least duplicate. This method was used in Examples 2 – 6.

A high pressure liquid chromatographic system equipped with a multi-solvent delivery system (Model 600E, Waters Associates, Milford, Mass.), an auto-injector (Model 717 Plus, Waters Ass.), a photodiode array detector (Model 996, Waters Ass.), a reverse phase Symmetric C_{18} column (150 mm x 3.9 mm ID, 5 µm), and a Millenium 2010 software computer system was used in this study. The mobile phases and UV wavelengths utilized for the analysis of diazepam, clonazepam, and (S)-2-carbamoyloxyl-1-o-chlorophenylethanol were 70% methanol, 30% water at 254 nm; 60% methanol, 40% water at 252 nm; and 25% acetonitrile, and 75% water at 262 nm, respectively.

Example 2

This example shows the effect of a bile salt and a lecithin dissolved in an aqueous medium at a 1% w/v level on the *in vitro* permeation of a model drug diazepam through the freshly excised nasal membrane. In these studies, a series of bile salts such as sodium cholate, sodium deoxycholate, sodium taurocholate, and sodium glycocholate, and a lecithin such as lysophosphatidylcholine were examined. The permeation rates were measured using the method described under the *in vitro* membrane permeation test method. The average steady-state transnasal flux data obtained in this manner are presented in Table I.

Table I

Effect of Bile Salts and Lecithin on the *In Vitro* Permeation of Diazepam across the Rabbit Nasal Mucosal Membrane at 37°C

Vehicle	Mean Transnasal Flux ($\mu g/cm^2/hr$) (n = 2)
Water	79.5
1% Sodium Cholate/H_2O	66.3
1% Sodium Deoxycholate/H_2O	74.9
1% Sodium Taurocholate/H_2O	87.0
1% Sodium Glycocholate/H_2O	96.4
1% Lysophosphotidylcholine/H_2O	125.5

As seen from Table I, a bile salt such as sodium glycocholate and a lecithin such as lysophosphotidylcholine produce a significant enhancing effect on the diazepam permeation through the nasal membrane.

Example 3

This example exhibits the influence of a vehicle on the *in vitro* membrane permeation of diazepam across the rabbit nasal mucous membrane at 37°C. In this experiment, a 1% diazepam suspension and solution were prepared using water and a co-solvent vehicle consisting of 30% ethanol (ETOH), 60% propylene glycol (PG), and 10% water (WT), respectively. The permeation rates were determined utilizing the method described in Example 1. The transnasal permeation profiles of diazepam obtained in this manner are presented in Fig. 1.

As seen from Fig. 1, a co-solvent vehicle comprising ethanol, propylene glycol, and water provides an approximately 8 times increase in the transnasal permeation rate of diazepam when compared with that obtained with an aqueous suspension.

Example 4

This example shows the influence of the drug concentration in the donor compartment on the permeation of diazepam through the nasal mucous membrane, *in vitro*. In this study, 0.5 – 2% diazepam formulations were prepared using a co-solvent mixture comprising 30% ethanol, 60% propylene glycol, and 10% water. The *in vitro* membrane permeation rates were measured using the test method described in Example 1. The *in vitro* transnasal flux data obtained with diazepam formulations over 0.5 – 2% level are shown in Fig. 2.

As seen from Fig 2, the steady-state transnasal flux of diazepam increases linearly with increasing the drug concentration in the donor compartment over the 0.5 – 2.0% concentration level.

Example 5

This example shows the effect of the incorporation of a bile salt into a nasal formulation according to the invention on the *in vitro* transnasal membrane permeation of diazepam. In this experiment, the inclusion of sodium glycocholate to a vehicle consisting of 30% ethanol, 60% propylene glycol, and 10% water at a 1% level was examined. Sample drug solutions (10 mg/ml) were prepared with the vehicle with and without the bile salt. The membrane permeation rates were measured in the use of the test method described in Example 1. The *in vitro* permeation profiles obtained in this manner are presented in Fig. 3.

As seen from Fig. 3, the inclusion of a 1% level of sodium glycocholate enhances the transnasal permeation rate of diazepam significantly. An approximately 50% increase in the steady-state flux is noticed when the bile salt is incorporated into the vehicle.

Example 6

This example shows the comparative transnasal permeabilities of three model drugs such as diazepam, clonazepam, and (S)-2-carbamoyloxyl-1-o-chlorophenylethanol. In this experiment, a co-solvent vehicle consisting of 30% ethanol, 60% propylene glycol, and 10% water was used. The *in vitro* permeation experiments were performed using the test method described in Example 1. The comparative transnasal permeability coefficient and steady-state flux data obtained with the medicaments at an initial drug concentration of 5mg/ml are presented in Table II.

Table II

Comparative Transnasal Permeability of Model Drug Substances across the Rabbit Nasal Mucous Membrane *In Vitro*

Drug Compound	Permeability Coefficient (cm/hr)	Transnasal Flux ($\mu g/cm^2/hr$)
Diazepam	4.92×10^{-2}	246.0
Clonazepam	6.95×10^{-2}	347.7
(S)-2-carbamoyloxyl-1-o-chlorophenylethanol	9.77×10^{-2}	487.6

As seen from Table II, the monocarbamate based anticonvulsant, (S)-2-carbamoyloxyl-1-o-chlorophenylethanol appears to have approximately two times greater transnasal permeability as compared with that of diazepam.

Example 7

Bioavailability and Pharmacokinetics of Diazepam Preparations

The bioavailability and pharmacokinetic characteristics of the preparations of the invention containing diazepam were tested after intranasal application to New Zealand White rabbits (n = 3-4). For comparison, a diazepam injection (Formula 1 on Table III) was examined *in vivo* after intravenous administration of the same dose. IV Formula 1

(10 mg/2 ml) was obtained from Elkins-Sinn, Inc., which was prepared with propylene glycol (0.4 ml), alcohol (0.1 ml), benzyl alcohol (0.015 ml), sodium benzoate/benzoic acid (50 mg), and a sufficient quantity of water for injection to make 1 ml. For intranasal application, two formulations were prepared using a vehicle system of the invention consisting of 30% ethanol, 60% propylene glycol, and 10% water with (Formula 3 on Table III) and without (Formula 2 on Table III) 1% sodium glycocholate, respectively. Another nasal formulation (Formula 4 on Table III), prepared with a non-ionic surfactant vehicle of polyoxyethylated castor oil (Cremophor EL), was also tested after intranasal application for comparison since this formulation was tested in humans by Lau and Slattery (1989). All of the nasal formulations were prepared just prior to the experiments by dissolving 20-mg diazepam (Sigma Chemical) in 1 ml of the vehicles described above.

Just prior to the experiment, rabbits (n=3-4) were weighed and restrained in rabbit restrainers while they were facing up. Each rabbit received 100 µl of the Formula 2 or 3 into each nostril by means of a Pfeiffer spray device within 5 seconds. Rabbits (n=3) having IV administration received 1mg/kg of Formula 1 as an ear-vein infusing during 20 seconds. For the repeated dosing studies, the same volume of Formula 3 (100µl) was sprayed into each nostril 5 minutes after the first dosing. Blood samples (1 ml) were collected at 0, 2, 5, 10, 20, 30, 45, 60, and 120 minutes after the IV and IN administration. From the blood samples, plasma was separated by centrifugation and stored at – 20°C until analysis. For analysis, plasma samples (0.5 ml) were accurately transferred into a 1.5 ml polypropylene centrifuge tube. To the plasma sample, 0.5 ml of 0.01% v/v perchloric acid in an acetonitrile containing internal standard (clonazepam 1 µg/ml) was added. The mixture was vortexed for 30 seconds and centrifuged at 4000 rpm for 10 minutes. The plasma concentration of diazepam was assayed by HPLC. The analysis was performed with the Waters HPLC as described in Example 1. The column used in this study was a 3.9 mm x 150 mm x 5 µm Symmetric C_{18} column. The mobile phase was 50% methanol: 10% acetonitrile: 40% pH 3.5 phosphate buffer by volume. The flow rate of the mobile phase was 1 ml/min and the UV detection was made at 228.5

nm. The detection limit for diazepam was 70 nmol/l. The areas (AUC) under the drug plasma concentration-time curves, from 0 min to 120 minutes, were calculated by means of the linear trapezoidal method. The bioavailability and pharmacokinetic data obtained in this manner are listed in Table III. The comparative pharmacokinetic profiles obtained after a single IV administration (Formula 1) and single and double IN applications of the preparations of the invention (Formulas 3 and 4) are depicted in Figs. 4 and 5, respectively.

Table III

Bioavailability and Pharmacokinetic Parameter of Diazepam after IV and IN Administration of the Preparation of the Invention in Rabbits

Route/ Formulation	Dosing (mg/kg)	C_{max} (ng/ml)	T_{max} (min)	A U C $_{(0-120\ min)}$ (ng x min/ml)	F (%)
IV Formula 1[a]	Single (1 mg/kg x 1)	398.8 (63.0)[d]	2.0	17582 (407)[d]	100.0 (n=3)
IN Formula 2[b]	Single (1 mg/kg x 1)	273.6 (62.2)[d]	5.0	10383 (692)[d]	59.1 (n=3)
IN Formula 3[c]	Single (1 mg/kg x 1)	273.7 (26.4)[d]	2.0	13300 (972)[d]	75.7 (n=4)
IN Formula 3[c]	Double[f] (1 mg/kg x 2)	327.1 (29.7)[d] 556.9 (130.5)[d]	2.0 10.0	26787 (4859)[d]	76.2[e] (n=3)
IN Formula 4[g]	Single (1 mg/kg x 1)	73.3 (11.9)[d]	30.0	7497 (1445)[d]	42.6 (n=3)

[a] IV Formula 1: 0.5% Diazepam Injection, USP, Elkins-Sinn, Inc., (PG / ETOH /Benzyl Alcohol / Sodium Benzoate/Benzoic Acid/Water for Injection)

[b] IN Formula 2: 2% Diazepam Solution in 60% PG, 30% ETOH, and 10% Water

[c] IN Formula 3: 2% Diazepam Solution in 1% SGC, 60% PG, 30% ETOH, and 10% Water

[d] Standard deviation

[e] Normalized data determined using the following equation:

$$F = \{AUC_{IN,\ 1\ mg\ x\ 2} / 2 \times AUC_{IV,\ 1\ mg\ x\ 1}\} \times 100\}$$

[f] Application time: t_{zero} : First dosing for nasal administration

$t_{5\ minutes}$: Second dosing for nasal administration

[g] IN Formula 4: 2% Diazepam Solution in Cremophor EL

As seen from Fig. 4 and Table III, IN Formula 3 prepared with 1% SGC, 30% ethanol, 60% PG, and 10% water increases the transnasal absorption markedly when compared with the Cremophor EL Formula 4. The C_{max} and $AUC_{0\text{-}120\ minutes}$ for the IN Formula 3 are approximately 69% and 76% with reference to the IV administration, respectively. On the other hand, the C_{max} and $AUC_{0\text{-}120\ minutes}$ for the Cremophor EL Formula 4 are about 19% and 42.6% of the IV injection. These comparative results appear to be consistent with the human pharmacokinetic data reported by Lau and Slattery (1989). According to the reported data, the Cremophor EL formulation yielded the T_{max} of 1.4 hours after intranasal administration in humans and the C_{max} was only about 27% relative to the IV injection . Surprisingly enough, as seen from Fig. 5 and Table III, a repeated intranasal application 5 minutes after the first dosing produces a marked increase in the transnasal absorption of diazepam. The C_{max} and AUC values were exactly doubled after the second application relative to those obtained with the first administration. In addition, the plasma diazepam level attained after the second dosing exceeds that of the single IV administration within 7 minutes. These findings clearly demonstrate that a repeated dosing regimen (within a short period of time) can be effectively utilized for the acute management of epileptic seizures when a single intranasal dosing is incapable of producing the desired therapeutic effect.

Example 8

Control of Peak Plasma Level Pharmacokinetics

Two mg of diazepam in a 100 µl vehicle was prepared and applied to rabbits (n=3) in a manner analogous to that described in Example 7. The following vehicles were tested: 60% ETOH, 30% PG, and 10% water (WT) with 1% SGC, 30% ETOH, 60% PG,

and 10% water (WT) with 1% SGC, and 20% ETOH, 70% PG and 10% water (WT) with 1% SGC. Blood samples were collected from the ear vein at the following time intervals: 0, 2, 5, 10, 20, 30, 45, 60, and 120 minutes. The diazepam concentration in plasma was determined by HPLC. The pharmacokinetic profiles obtained after IV and IN administration of the preparations are presented in Table IV and Fig. 6.

Table IV

Effect of ETOH/PG Volume Ratio of the Vehicle on the Pharmacokinetic Parameter of Diazepam after IV and IN Administration of the Preparation of the Invention in Rabbits

Route/ Formulation	Dosing (mg/kg)	C_{max} (ng/ml)	T_{max} (min)	A U C $_{(0-120\ min)}$ (ng x min/ml)	F (%)
IV Formula 1[a]	Single (1 mg/kg x 1)	398.8 (63.0)[e]	2.0	17582 (407)[e]	100.0 (n=3)
IN Formula A[b]	Single (1 mg/kg x 1)	313.2 (17.3)[e]	2.0	13592 (692)[e]	77.3 (n=3)
IN Formula B[c]	Single (1 mg/kg x 1)	273.7 (26.4)[e]	2.0	13300 (972)[e]	75.7 (n=4)
IN Formula C[d]	Single (1 mg/kg x 1)	246.3 (32.2)[e]	2.0	12860 (827)[e]	73.1 (n=3)

[a] IV Formula 1: 0.5% Diazepam Injection, USP, Elkins-Sinn, Inc., (PG / ETOH /Benzyl Alcohol / Sodium Benzoate/Benzoic Acid/Water for Injection)

[b] IN Formula A: 2% Diazepam Solution in 1% SGC, 30% PG, 60% ETOH, and 10% Water

[c] IN Formula B: 2% Diazepam Solution in 1% SGC, 60% PG, 30% ETOH, and 10% Water

[d] IN Formula C: 2% Diazepam Solution in 1% SGC, 70% PG, 20% ETOH, and 10% Water

[e] Standard deviation

As seen from Table IV and Fig. 6, the peak plasma concentration of the drug, observed within 2 minutes after the IN administration, can be controlled depending on the ETOH/PG volume ratio in the vehicles examined. The C_{max} increases gradually with increasing the ETOH/PG volume ratio from 0.3 to 2. In addition, the peak plasma concentration for the IN vehicle consisting of 60% ETOH, 30% PG and 10% water (WT) with 1% SGC at 2 minutes is approximately 79% of an IV injection of the same dose.

In addition, modulating the ETOH/PG volume ratio in the vehicles can also control the plasma level-time profile in the elimination phase.

Example 9

Pharmacological Response of Diazepam Preparations

The pharmacological response was examined in New Zealand White rabbits by evaluating the muscle relaxation effect of diazepam after IV administration and IN administration of the preparations of the invention at a dosing level of 1 mg/kg. The vehicle of nasal formulation consisted of 30% ethanol, 60% propylene glycol, and 10% water containing 1% SGC. The sample formulation was prepared by dissolving 20 mg diazepam in 1 mL of the vehicle by ultrasonification. The IV formulation was the same as that used in Example 7. The pharmacological response was measured in rabbits after application of 100 μL of nasal formulation into each nostril while the rabbit was in a lying position after being firmly tipped with a finger on the hip. The mean response times that the rabbits remained in a lying position with its hind legs stretched to one side after IV and IN administration are listed in Table V.

Table V

Mean Pharmacological Response Times after IV and IN Administration of Diazepam Preparations

Route/Formulation	Response Time (Min.)	N
IV Injection	1.1 ± 0.2	3

IN Formula 3	1.5 ± 0.5	3

As seen from Table V, the nasal formulation of the invention provides a very fast response. The time to pharmacological response was 1.5 minutes.

Example 10

Bioavailability and Pharmacokinetics of Clonazepam Preparations

An intranasal formulation was prepared by dissolving 8.36 mg clonazepam in 2 ml of a vehicle of the invention consisting of 30% ETOH, 60% PG, and 10% water containing 1% SGC. A formulation for IV injection was prepared by dissolving 3-mg of clonazepam in 2 mL of a 40% PG, 30% ETOH, and 30% water solution and filtering the solution through a sterile filter under aseptic conditions. The formulations were administered to rabbits (n=3) at a dose of 0.2 mg/kg in a manner analogous to those described in Example 7. A repeated dosing regimen (double and triple applications) at 5 minutes time intervals was also tested. Blood samples were obtained from the ear vein at the following time intervals: 0, 2, 5, 10, 20, 30, 45, 60, and 120 minutes. From the blood samples, plasma was separated by centrifugation and stored at – 20°C until analysis. For analysis, plasma samples (0.5 ml) were accurately transferred into a 15-ml test tube. To the plasma sample, 10µl of an internal standard solution (diazepam - 5 µg/ml) and 50µl NaOH (0.5M) were added. To the above mixture, 5 ml of diethyl ether was added and this mixture was vortexed for 60 seconds and centrifuged at 4000 rpm for 10 minutes. The upper ethereal solution was transferred to a 5 ml test tube and evaporated in a vacuum evaporator at 40°C for 30 minutes. The residue was reconstituted with 100 µl of the mobile phase for HPLC analysis consisting of 20% methanol, 30% acetonitrile, and a 50% pH 3.5 KH_2PO_4/H_3PO_4 buffer solution. The clonazepam concentration in the plasma was determined by HPLC using a flow rate of 1 ml/minute and the UV detection at 254 nm. The detection limit for clonazepam was 16 nmol/l. The bioavailability and pharmacokinetic data obtained after IV and IN administration in a single or multiple

dosing schedule are listed in Table VI and the mean plasma concentration-time profiles are shown in Fig. 7.

Table VI

Bioavailability and Pharmacokinetic Parameters for Clonazepam after IV and IN Administration of the Preparations to Rabbits

Route/ Formulation	Dosing (mg/kg)	C_{max} (ng/ml)	T_{max} (min)	A U C $_{(0-120\ min)}$ (ng x min/ml)	F (%)
IV Formula[a]	Single (0.2mg/kg x 1)	104.8	2.0	7437.7	100.0 (n=2)
IN Formula[b]	Single (0.2mg/kg x 1)	32.9 (5.9)[c]	2.0	3356.4 (544.8)[c]	45.1 (n=3)
IN Formula[b]	Double[f] (0.2mg/kg x 2)	49.5 (5.3)[c]	10.0	4896.8 (836.6)[c]	32.9[d] (n=3)
IN Formula[b]	Triple[f] (0.2mg/kg x 3)	80.2 (21.3)[c]	15.0	7766.1 (2077.9)c	34.8[e] (n=3)

[a] IV Formula: 0.15% Clonazepam Solution in 40% PG, 30% ETOH and 30% Water
[b] IN Formula: 0.42% Clonazepam Solution in 1% SGC, 60% PG, 30% ETOH, and 10% Water
[c] Standard deviation
[d] Normalized data calculated using the following equation:
$F = \{AUC_{IN,\ 0.2\ mg\ x\ 2}/2 \times AUC_{IV,\ 0.2\ mg\ x\ 1}\} \times 100$
[e] Nomalized data calculated using the following equation:
$F = \{AUC_{IN,\ 0.2mg\ x\ 3}/3 \times AUC_{IV,\ 0.2\ mg\ x\ 1}\} \times 100$
[f] Application times: t_{zero}: First dosing for nasal administration
$t_{5\ minutes}$: Second dosing for nasal administration
$t_{10\ minutes}$: Third dosing for nasal administration

As seen from Table VI and Fig. 7, the initial peak plasma concentration is attained within 2 minutes after the first intranasal application of the preparation. The peak plasma level was about 32% of the IV injection. However, after the third application at 5

minutes intervals, the peak plasma concentration observed at 15 minutes was nearly identical to that of the single IV injection of clonazepam.

Example 11

Pharmacological Response of Clonazepam Preparations

The pharmacological response of clonazepam preparations was examined in New Zealand White rabbits after application of 100 μL of the 4.18 mg clonazepam/mL vehicle into each nostril in a manner analogous to that described in Example 9. The vehicle consisted of 30% ETOH, 60% PG, and 10% water containing 1% SGC. Clonazepam was dissolved in the vehicle by ultrasonification. The IV formulation used in the study was the same as described in Example 10. The mean response times measured after the IV and IN administration are presented in Table VII.

Table VII

Mean Pharmacological Response Times after IV and IN Administration of Clonazepam Preparations

Route/Formulation	Response Time (Minutes)	N
IV Injection	1.7 ± 0.5	3
IN Formulation	1.4 ± 0.7	3

As shown in Table VII, the intranasal application of the clonazepam formulation of the invention provides a faster response time (1.4 minutes) when compared with that of IV injection (1.7 minutes).

Example 12

Bioavailability and Pharmacokinetics of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol Preparations

An intranasal formulation was prepared by dissolving 50 mg or 100 mg of a monocarbamate based new anticonvulsive agent (S)-2-carbamoyloxyl-1-o-chlorophenylethanol in 1 mL of a vehicle of the invention consisting of 30% ETOH, 60% PG, and 10% water containing 1% SGC. A formulation for IV injection was prepared by dissolving 15 mg (S)-2-carbamoyloxyl-1-o-chlorophenylethanol in 1 mL of 40% PEG 400 and 60% water and filtering through a sterile membrane filter under aseptic conditions. The formulations were administered to rabbits (n = 2-4) at the two dosing levels of 2.5 mg/kg and 5 mg/kg in a manner analogous to that described in Example 7. A repeated dosing regimen at 5 minute intervals was also studied in the nasal application of the preparation of the invention. Blood samples were obtained from the ear vein at the following time intervals: 0, 2, 5, 10, 20, 30, 45, 60, 120, 180 and 240 minutes. From the blood samples, plasma was separated by centrifugation and stored at – 20°C until analysis. For analysis, plasma samples (0.5 ml) were accurately transferred into a 15-ml test tube. To the plasma sample, 50µl of an internal standard solution (2-(2,6-dichlorophenyl)-2-carbamoyloxyethyl)oxocarboxamide - 10 µg/ml) and 5 ml of methyl-butyl ether were added. The mixture was vortexed for 60 seconds and centrifuged at 3500 rpm for 10 minutes. The upper ethereal solution was transferred to a 5 ml test tube and evaporated in a vacuum evaporator at 40°C for 30 minutes. The residue was reconstituted with 200 µl of deionized water. The (S)-2-carbamoyloxyl-1-o-chlorophenylethanol concentration in the plasma was determined by HPLC in the use of a mobile phase consisting of 20% acetonitrile and 80% water with a flow rate of 1 ml/minute and UV detection at 210 nm. The detection limit for (S)-2-carbamoyloxyl-1-o-chlorophenylethanol was 23 nmol/l. The pharmacokinetic parameters determined after IV and IN administration of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol at two dose strengths are presented in Table VIII. The bioavailability and pharmacokinetic parameters obtained after IV administration and IN administration of the preparations of the invention in a single and double dosing regimen are listed in Table IX. The mean plasma concentration-time profiles obtained after IV and IN administration of (S)-2-

carbamoyloxyl-1-o-chlorophenylethanol preparations in single and double dosing schedules are presented in Figs. 8 and 9.

Table VIII

Pharmacokinetic Parameters of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol after a Single IV and IN Administration at Two Dosing Strengths

Route/ Formulation	Dose (mg/kg)	Maximum Conc.(ng/ml)	T_{max} (min)	AUC $_{(0-240\ min)}$ (ng x min/ml)	F (%)
IV Formula[a]	5.0	6267.7 (408.0)[d]	2.0	473176 (56105)[d]	100.0 (n=4)
IN Formula 1[b]	5.0	2404.9. (130.0)[d]	30.0	373991 (5077)[d]	79.1 (n=3)
IV Formula[a]	2.5	4179.9	2.0	221291	100.0 (n=2)
IN Formula 2[c]	2.5	1407.2	5.0	160269	72.4 (n=2)

[a] IV Formula : 1.5 % (S)-2-carbamoyloxyl-1-o-chlorophenylethanol solution in 40% PEG 400 and 60% Water

[b] IN Formula 1: 10% (S)-2-carbamoyloxyl-1-o-chlorophenylethanol solution in 1% SGC, 60% PG, 30% ETOH and 10% Water

[c] IN Formula 2: 5% (S)-2-carbamoyloxyl-1-o-chlorophenylethanol solution in 1% SGC, 60% PG, 30% ETOH, and 10% Water

[d] Standard deviation

Table IX

Bioavailability and Pharmacokinetic Parameters of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol after IV and IN Administration of the Preparations in Single and Double Dosing Regimen

Route/ Formulation	Dose (mg/kg)	Maximum Conc.(ng/ml)	T_{max} (min)	A U C $_{(0-240\ min)}$ (ng x min/ml)	F (%)
IV Formula[a]	Single (5 mg/kg x 1)	6267.7 (408.0)[c]	2.0	473176 (56105)[c]	100.0 (n=4)
IN Formula[b]	Single (5 mg/kg x 1)	2404.9. (130.0)[c]	30.0	373991 (5077)[c]	79.1 (n=3)
IN Formula [b]	Double[e] (5 mg/kg x 2)	4332.3 (979.3)[c]	30.0	700475 (114195)[c]	74.0[d] (n=3)

[a] IV Formula: 1.5% (S)-2-carbamoyloxyl-1-o-chlorophenylethanol solution in 40% PEG 400, and 60% Water

[b] IN Formula : 10% (S)-2-carbamoyloxyl-1-o-chlorophenylethanol solution in 1% SGC 60% PG, 30% ETOH, and 10% Water

[c] Standard deviation

[d] Normalized data determined using the following equation:

$F = \{AUC_{IN,\ 5mg\ x\ 2}/2 \times AUC_{IV,\ 5\ mg\ x\ 1)} \times 100\}$

[e] Application times: t_{zero}: First dosing for nasal administration

$t_{5\ minutes}$: Second dosing for nasal administration

As seen from Table XIII, after the intranasal application the initial peak concentrations observed within 5 - 30 minutes increased proportionally with increasing the dose strength. The bioavailability of the nasal preparations is found to be 73-79% of the IV injection. The pharmacokinetic results presented in Table IX and Fig. 9 clearly demonstrate that the second application of the intranasal formulation 5 minutes after the first dosing produces a nearly identical bioavailability to that obtained after the first dosing. The C_{max} and $AUC_{0-240\ minutes}$ are doubled after the second intranasal application. In addition, the plasma concentration of (S)-2-carbamoyloxyl-1-o-chlorophenylethanol

achieved after the second dosing exceeded the plasma level obtained with a single IV injection at 30 minutes.

Example 13

Stability Studies

In an effort to optimize the stability of the medicaments in the pharmaceutical compositions according to the present invention, an accelerated stability study was performed at a storage temperature of 37°C over a 10 - 14 weeks time period. Sample drug solutions (0.1 mg/ml) were prepared using a vehicle of the invention consisting of 30% ETOH, 60% PG, and 10% water. The drug solutions were stored in an oven set at 37°C. At appropriate time intervals, a 100 µl sample was withdrawn and analyzed by means of HPLC. The chemical stability data determined in terms of the percent drug recovery are presented in Table X.

Table X

Chemical Stability of the Preparations of the Invention at 37°C.

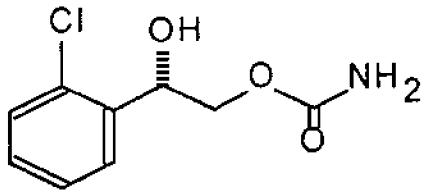
Drug Formulation	Storage Time (Weeks)	% Recovery
Diazepam Formulation	0	100.0
	4	100.3
	10	102.4
	14	102.6
Clonazepam Formulation	0	100.0
	4	101.7
	11	100.9
(S)-2-carbamoyloxyl-1-o-chlorophenylethanol Formulation	0	100.0
	3	100.2
	4	98.2
	9	98.0
	12	97.6

WHAT IS CLAIMED IS:

1. A method for administering a therapeutically effective amount of an anticonvulsive agent to the mucosal membranes of a mammal in a rate-controlled manner of absorption by means of a pharmaceutical composition comprising a therapeutically effective amount of the medicament dissolved or dispersed in a water-containing vehicle containing 10-80% by volume of an aliphatic alcohol, 10-80% by volume of a glycol and 0.1-5% by weight of a bile salt or a lecithin.

2. The composition of Claim 1, wherein the anticonvulsive agent is selected from the group consisting of diazepam, clonazepam, lorazepam , phenytoin, mephenytoin, ethotoin, phenobarbital, mephobarbital, primidone, carbamazepine, ethosuximide, valproic acid, trimethadione, gabapentin, lamotrigine, felbamate, γ-vinyl GABA, and acetazolamide.

3 The composition of Claim 1, wherein the anticonvulsive agent comprises a mono-carbamate anticonvulsive agent (S)-2-carbamoyloxyl-1-o-chlorophenylethanol by the following formula:



4. The composition of Claim 1, wherein the alcohol comprises an aliphatic alcohol containing 1 to 5 carbons.

5. The composition of Claim 1, wherein the glycol is selected from the group consisting of propylene glycol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, and polyethylene glycol 600.

6. The composition of Claim 1, wherein the bile salt is selected from the group consisting of sodium cholate, sodium deoxycholate, sodium glycocholate, sodium taurocholate, and sodium ursodeoxycholate.

7. The composition of Claim 1, wherein the lecithin is selected from the group consisting of lysophosphatidylcholines, phosphatidylcholines, phosphatidylserines, phosphatidylinositols, phosphatidylethanolamines, and phosphatidylglycerols.

8. A method for providing absorption in a rate-controlled manner in a mammal through the nasal administration of a pharmaceutical composition comprising a therapeutically effective amount of an anticonvulsant agent by modulating the aliphatic alcohol/glycol volume ratio in an intranasal vehicle system.

9. The method of Claim 8, wherein the anticonvulsant agent is dissolved or dispersed in the intranasal vehicle system to produce a rapid onset and a high plasma concentration level of medicament by increasing the aliphatic alcohol/glycol volume ratio in the vehicle from 0.1 to 8.0.

10. The method of Claim 8, wherein the anticonvulsant agent is dissolved or dispersed in the intranasal vehicle system to produce a rapid onset and a prolonged plasma concentration level of medicament by reducing the aliphatic alcohol/glycol volume ratio in the vehicle from 8.0 to 0.1.

11. The method of Claim 8, wherein the pharmaceutical composition comprising the anticonvulsive agent and the intranasal vehicle system is intranasally administered to a mammal in an amount effective for the treatment of epilepsy or other fever-induced seizures using single or multiple dosing regimens.

Fig. 1

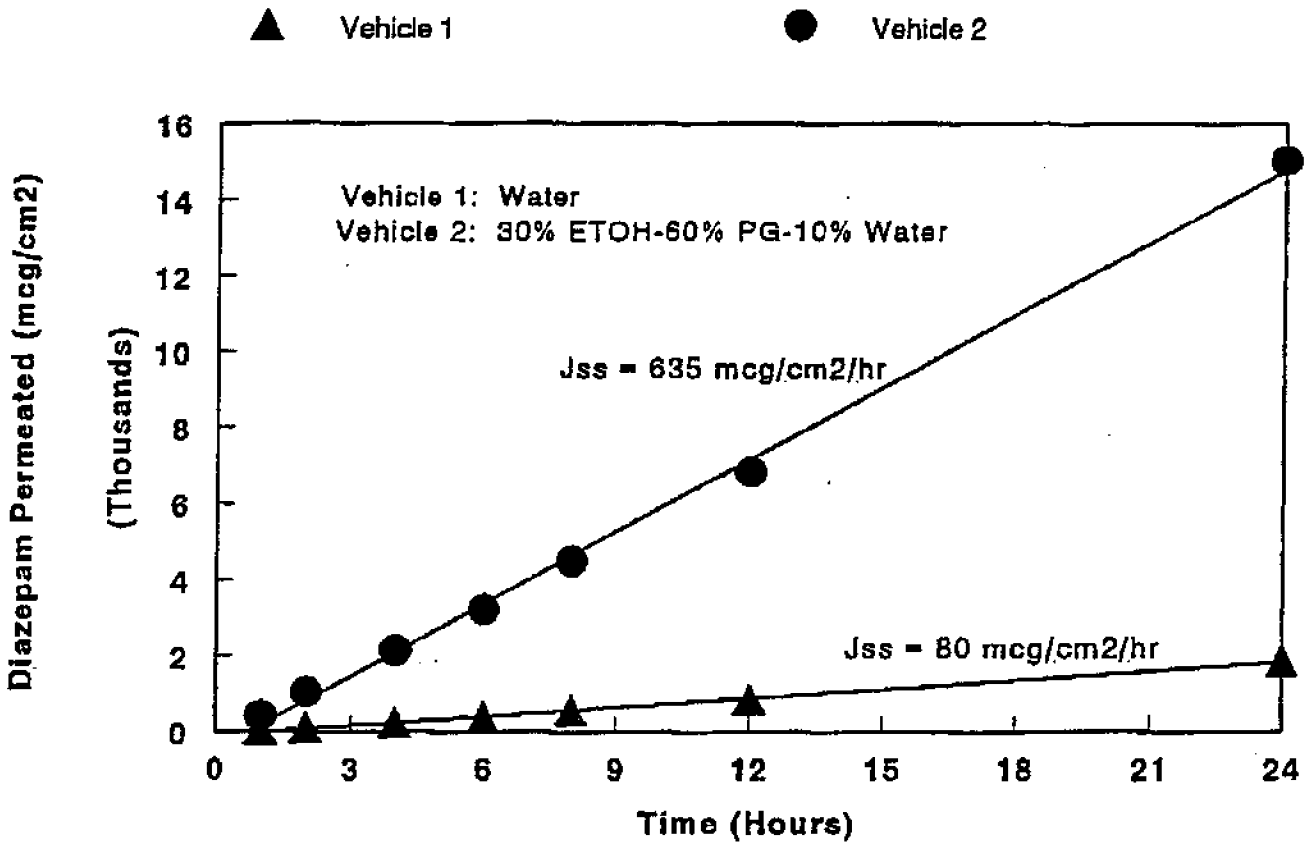

Vehicle 1
Vehicle 2
Vehicle 1: Water
Vehicle 2: 30% ETOH-60% PG-10% Water
Jss = 635 mcg/cm2/hr
Jss = 80 mcg/cm2/hr
Diazepam Permeated (mcg/cm2) (Thousands)
Time (Hours)
0
2
4
6
8
10
12
14
16
0
3
6
9
12
15
18
21
24

Fig. 2

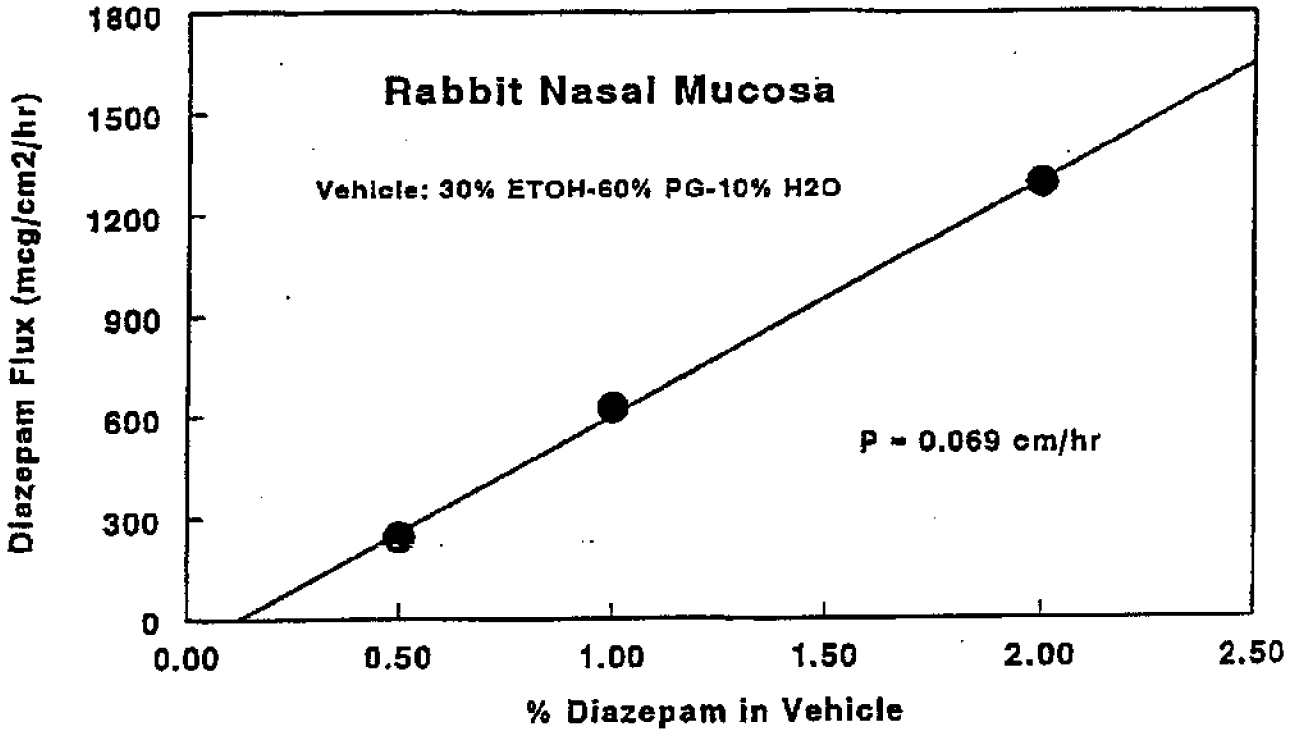

Rabbit Nasal Mucosa
Vehicle: 30% ETOH-60% PG-10% H2O
P = 0.069 cm/hr
Diazepam Flux (mcg/cm2/hr)
1800
1500
1200
900
600
300
0
0.00
0.50
1.00
1.50
2.00
2.50
% Diazepam in Vehicle

Fig.3

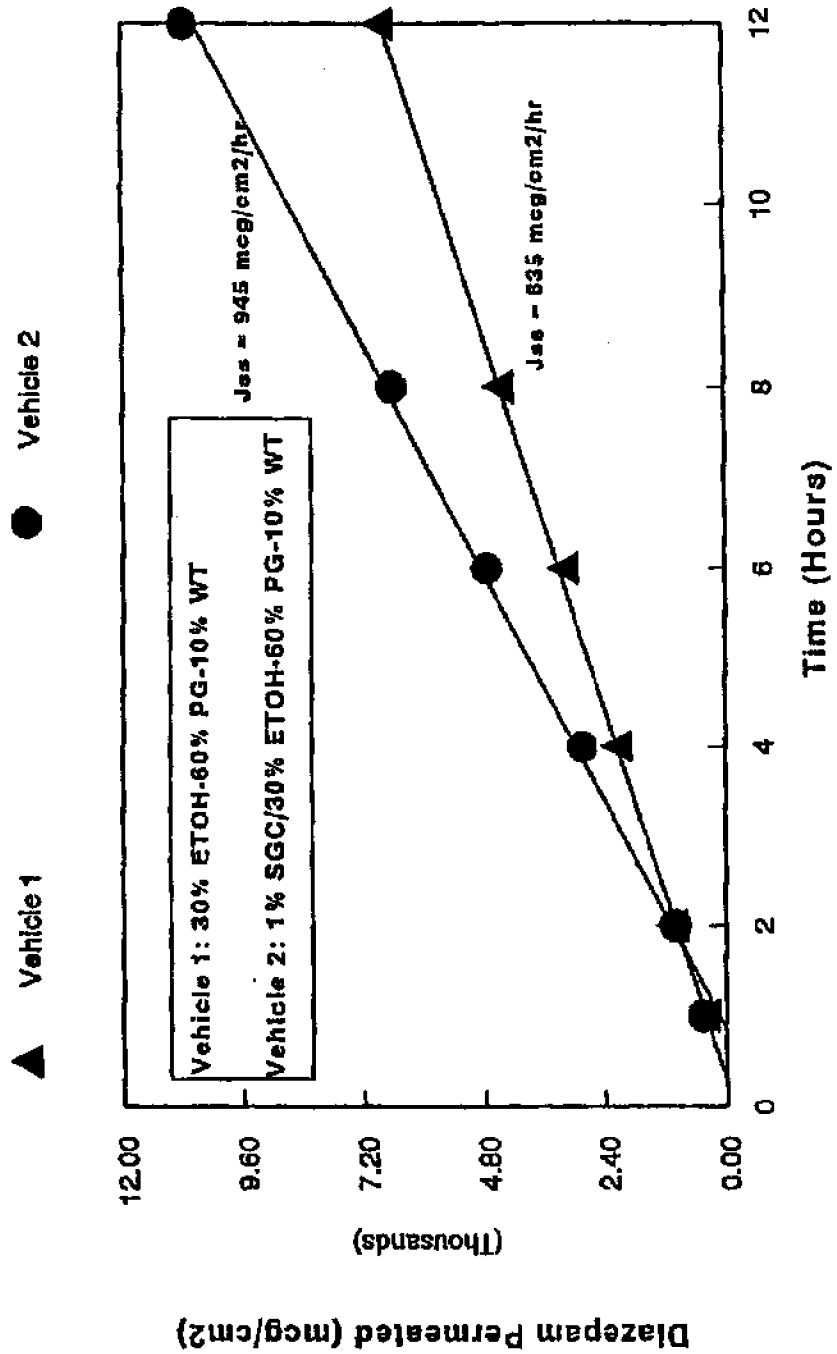

Vehicle 1
Vehicle 2
Vehicle 1: 30% ETOH-60% PG-10% WT
Vehicle 2: 1% SGC/30% ETOH-60% PG-10% WT
Jss = 945 mcg/cm2/hr
Jss = 635 mcg/cm2/hr
Diazepam Permeated (mcg/cm2)
(Thousands)
12.00
9.60
7.20
4.80
2.40
0.00
Time (Hours)
0
2
4
6
8
10
12

Fig. 4

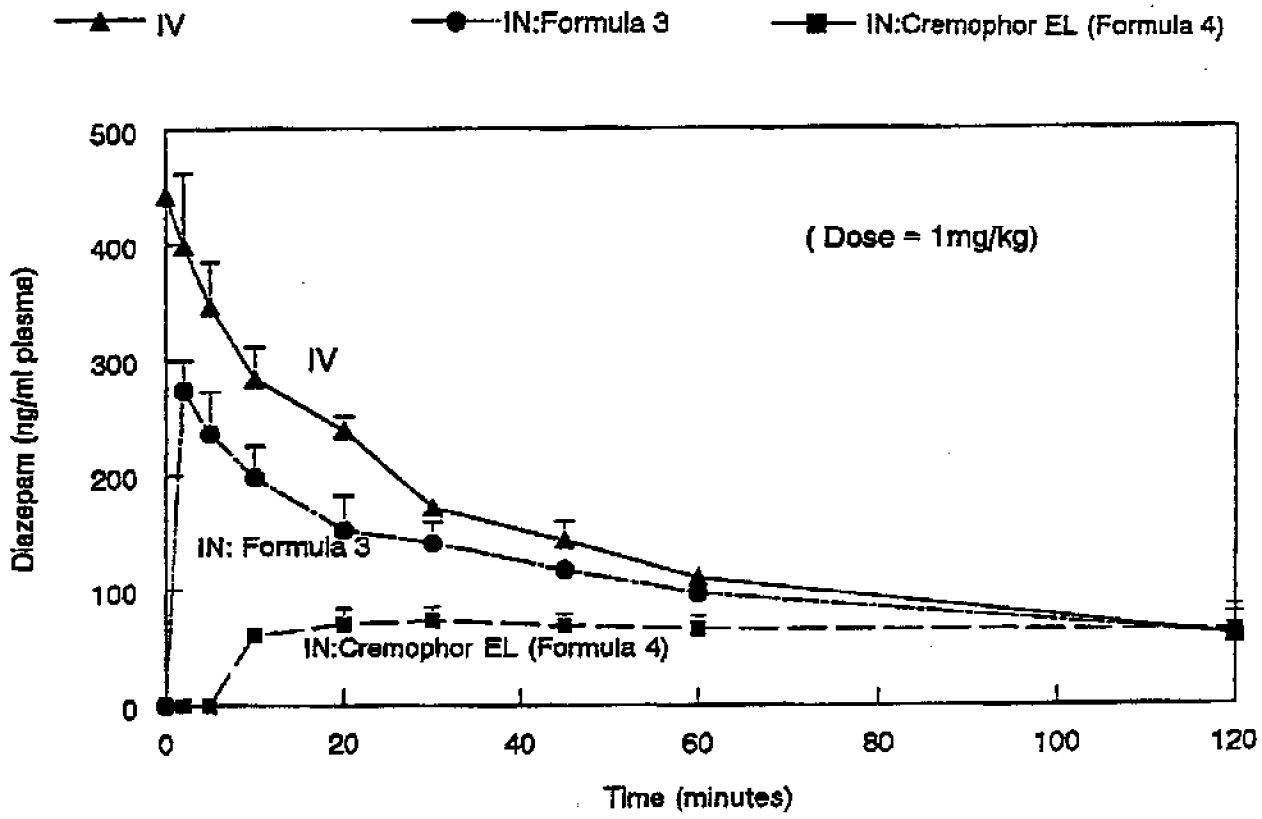

IV
IN:Formula 3
IN:Cremophor EL (Formula 4)
Diazepam (ng/ml plasma)
500
400
300
200
100
0
(Dose = 1mg/kg)
IV
IN: Formula 3
IN:Cremophor EL (Formula 4)
0
20
40
60
80
100
120
Time (minutes)

Fig. 5

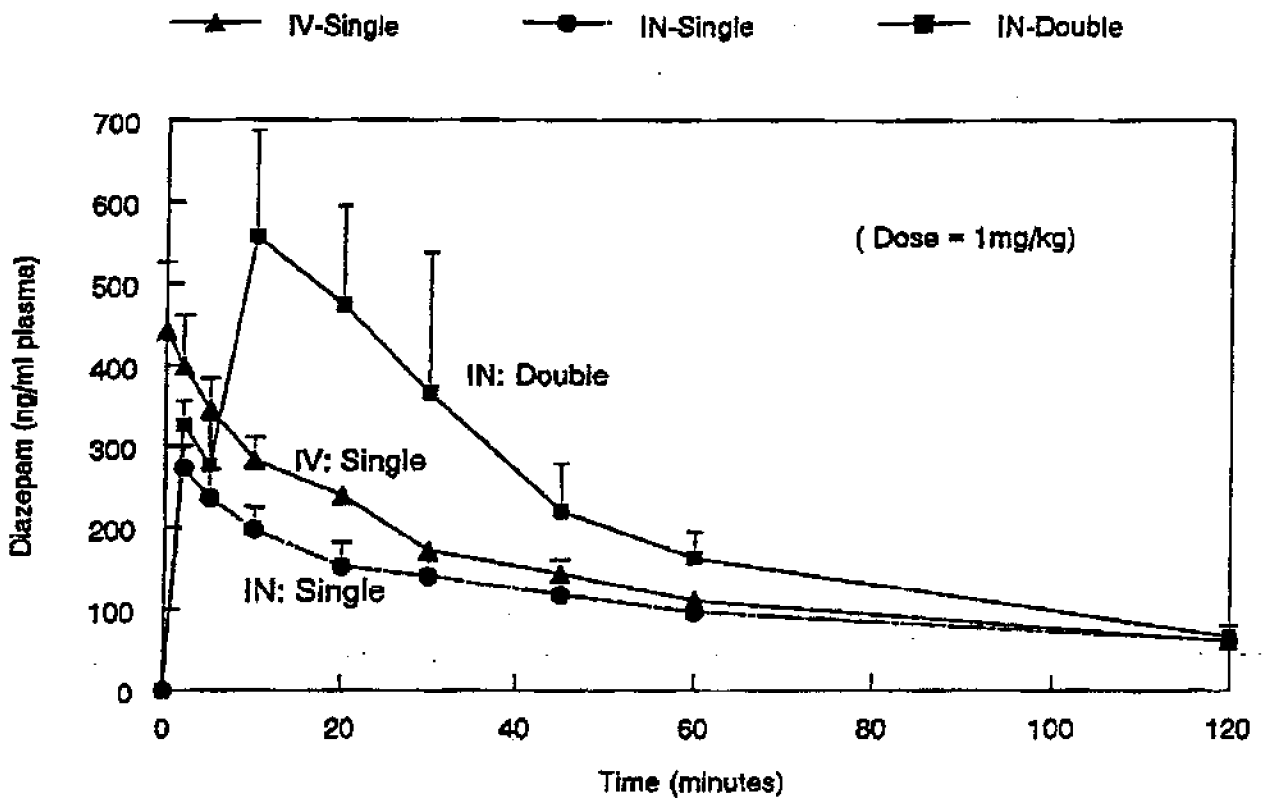

IV-Single
IN-Single
IN-Double
(Dose = 1mg/kg)
IN: Double
IV: Single
IN: Single
Diazepam (ng/ml plasma)
Time (minutes)
0
100
200
300
400
500
600
700
0
20
40
60
80
100
120

Fig. 6

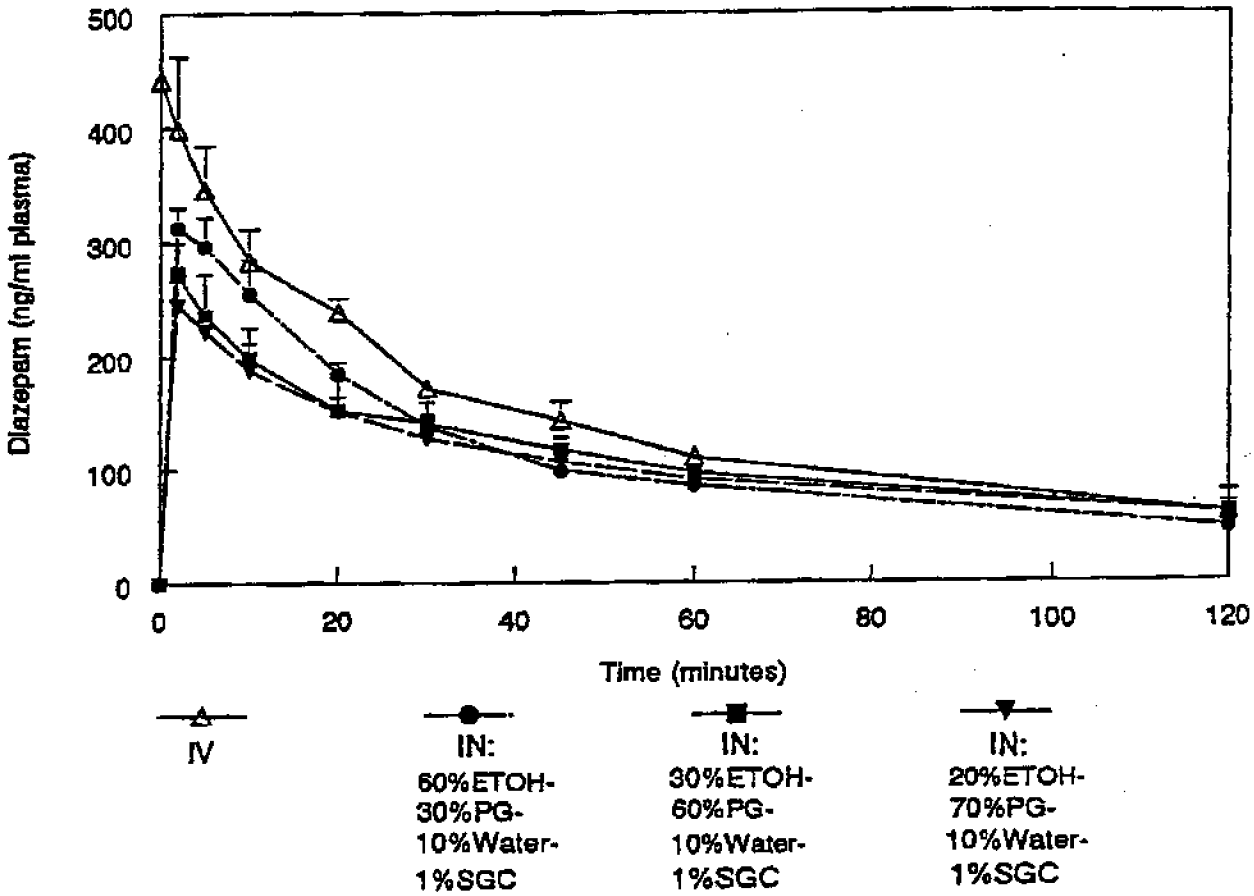

Diazepam (ng/ml plasma)
500
400
300
200
100
0
0
20
40
60
80
100
120
Time (minutes)
IV
IN: 60%ETOH-30%PG-10%Water-1%SGC
IN: 30%ETOH-60%PG-10%Water-1%SGC
IN: 20%ETOH-70%PG-10%Water-1%SGC

Fig. 7

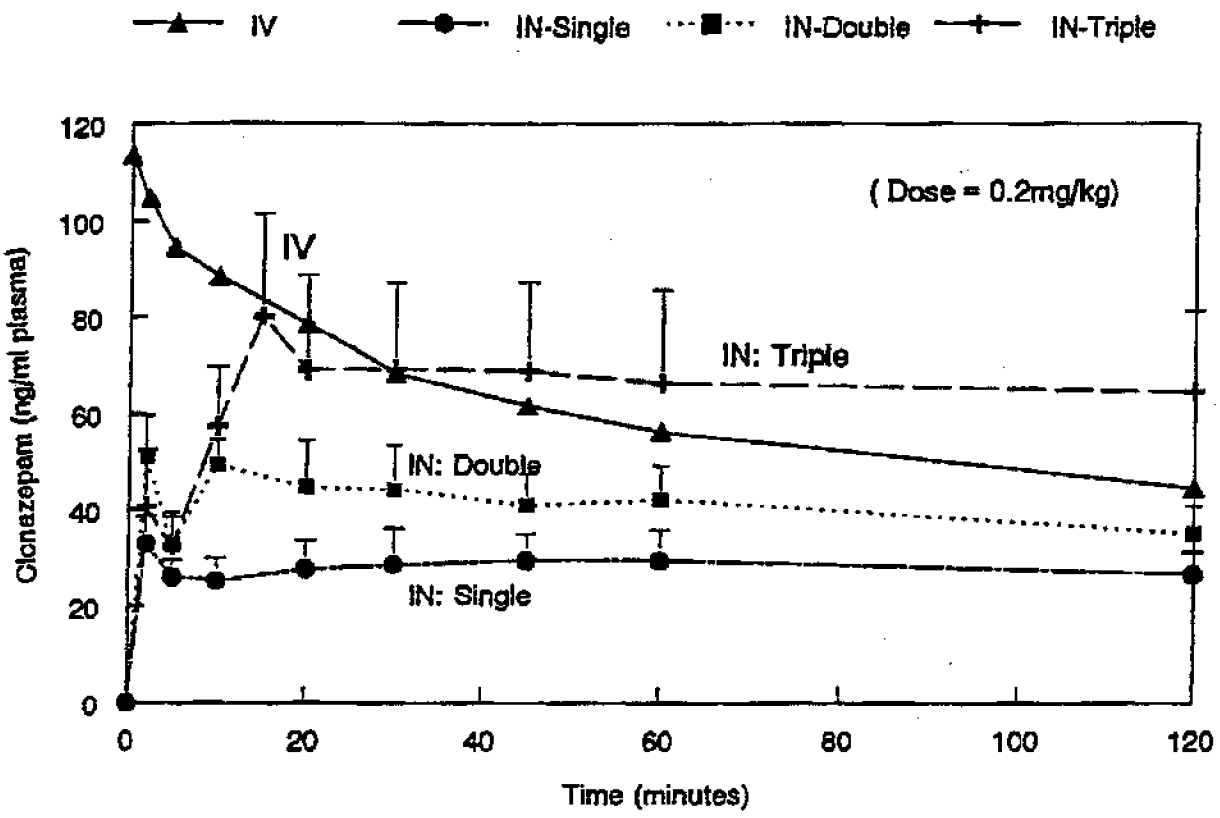

IV
IN-Single
IN-Double
IN-Triple
(Dose = 0.2mg/kg)
IV
IN: Triple
IN: Double
IN: Single
Clonazepam (ng/ml plasma)
Time (minutes)
0
20
40
60
80
100
120

Fig. 8

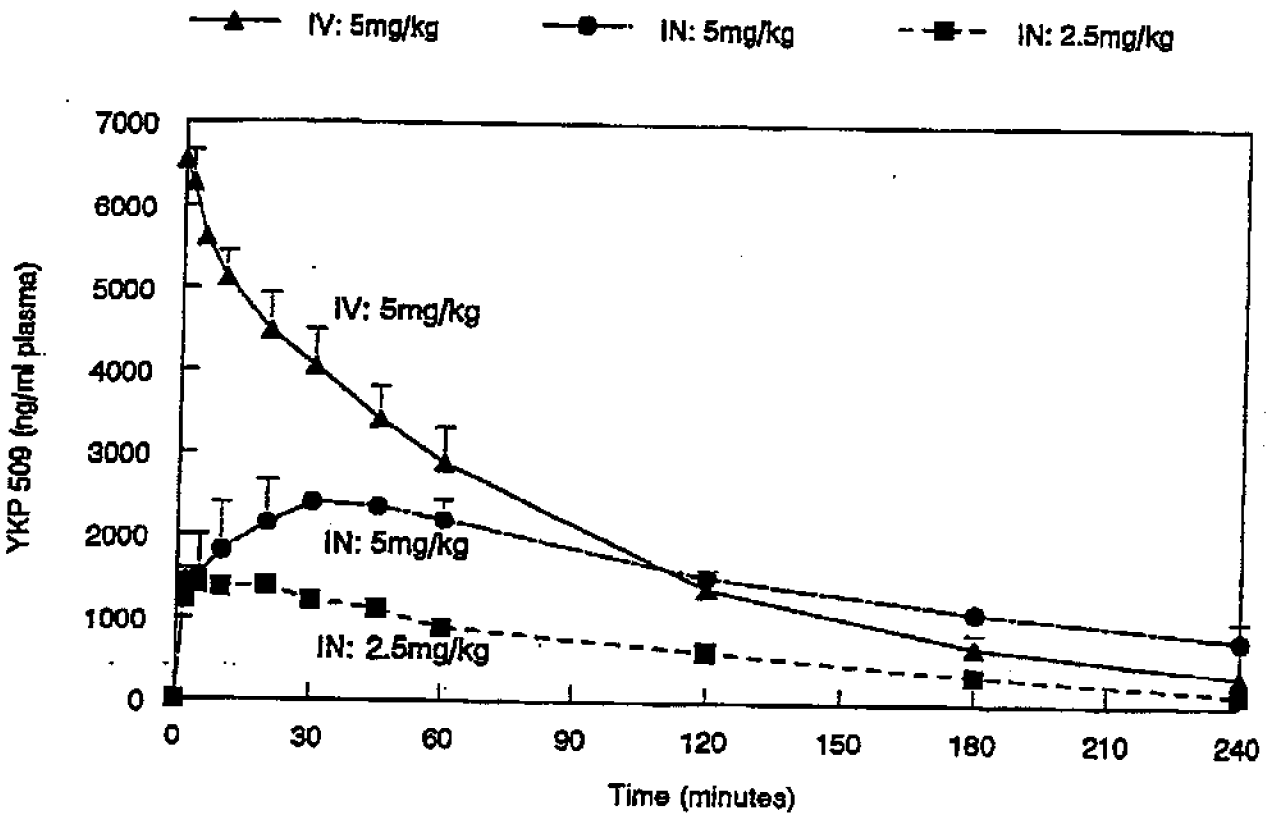
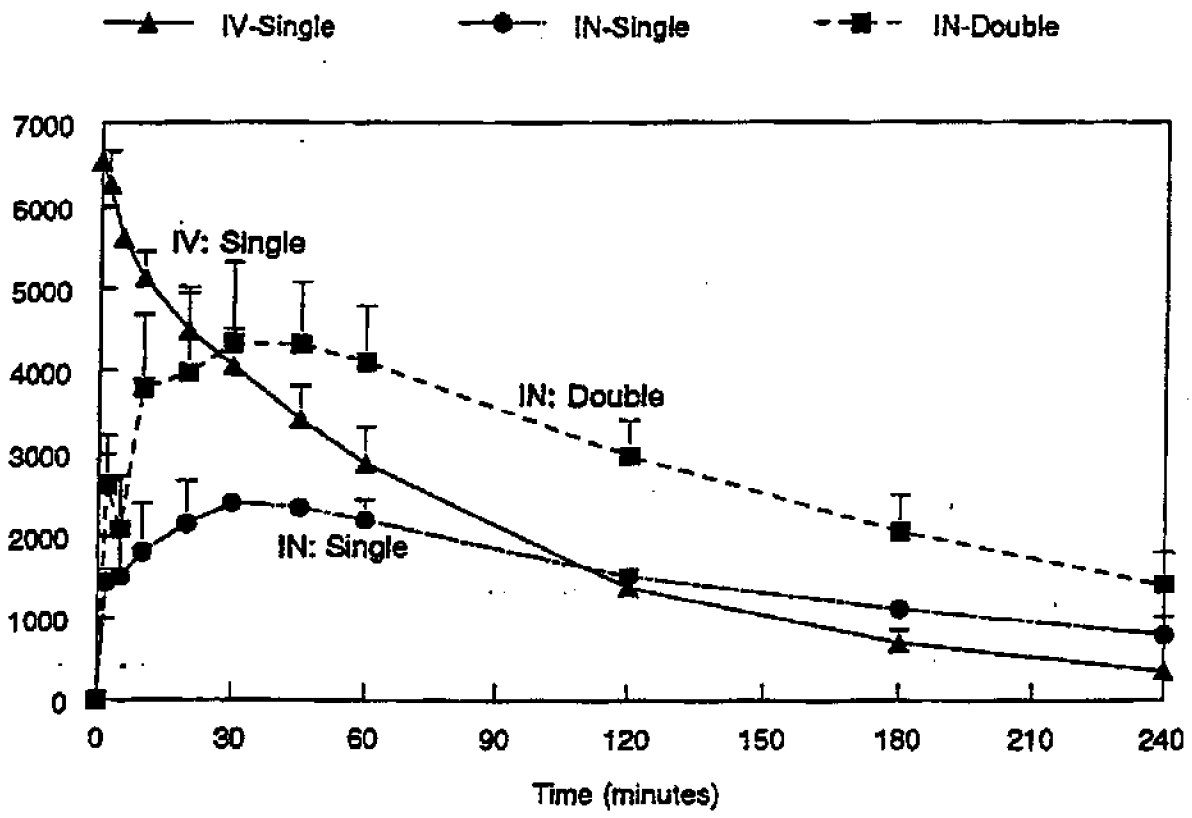

IV: 5mg/kg
IN: 5mg/kg
IN: 2.5mg/kg
YKP 509 (ng/ml plasma)
7000
6000
5000
4000
3000
2000
1000
0
IV: 5mg/kg
IN: 5mg/kg
IN: 2.5mg/kg
0
30
60
90
120
150
180
210
240
Time (minutes)

Fig. 9


IV-Single
IN-Single
IN-Double
7000
6000
5000
4000
3000
2000
1000
0
IV: Single
IN: Double
IN: Single
0
30
60
90
120
150
180
210
240
Time (minutes)

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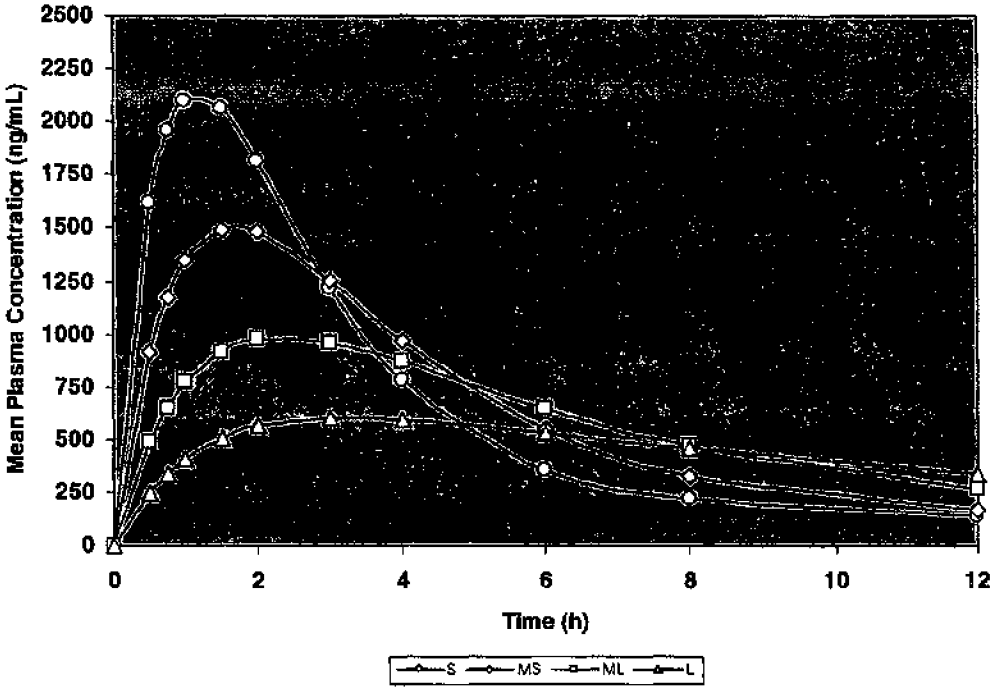
(54) Title: COMPOSITIONS HAVING A COMBINATION OF IMMEDIATE RELEASE AND CONTROLLED RELEASE CHARACTERISTICS



(57) Abstract: Disclosed are compositions exhibiting a combination of immediate release and controlled release characteristics. The compositions comprise at least one poorly soluble active ingredient having a nanoparticulate particle size, at least one surface stabilizer adsorbed onto the surface of the nanoparticulate active agent particles, and at least one active ingredient having a microparticulate particle size.

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COMPOSITIONS HAVING A COMBINATION OF IMMEDIATE RELEASE AND CONTROLLED RELEASE CHARACTERISTICS

FIELD OF THE INVENTION

The present invention relates to compositions exhibiting a combination of immediate release and controlled release characteristics. The compositions comprise at least one poorly soluble active ingredient having a nanoparticulate particle size, at least one surface stabilizer adsorbed onto the surface of the nanoparticulate active agent particles, and at least one poorly soluble active ingredient having a microparticulate particle size.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Compositions

Nanoparticulate compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble active agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent also describes methods of making such nanoparticulate compositions. Nanoparticulate compositions are desirable because with a decrease in particle size, and a consequent increase in surface area, a composition is rapidly dissolved and absorbed following administration. Methods of making such compositions are described in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances," U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described in, for example, U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for

"Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,187 for "Method of Grinding Pharmaceutical Substances;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices

With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydropropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" and 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," all of which are specifically incorporated by

reference. In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference.

Amorphous small particle compositions are described in, for example, U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent," 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds," 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds," 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods," and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter.

None of these references, or any other reference that describes nanoparticulate compositions, relates to a nanoparticulate composition having a combination of immediate release and controlled release characteristics.

B. Background Regarding Immediate Release Compositions

Conventional immediate release dosage forms, also referred to as "fast melt" or "rapidly disintegrating" dosage forms, rely on the composition of the drug matrix to effect the rapid release of the component active agent particles, rather than the particle size of the component active agent particles.

Current manufacturers of rapidly disintegrating or dissolving solid dose oral formulations include Cima Labs, Fuisz Technologies Ltd., Prographarm, R.P. Scherer, and Yamanouchi-Shaklee. All of these manufacturers market different types of rapidly dissolving solid oral dosage forms.

Cima Labs markets OraSolv®, which is an effervescent direct compression tablet having an oral dissolution time of five to thirty seconds, and DuraSolv®, which is a direct compression tablet having a taste-masked active agent and an oral dissolution time of 15 to 45 seconds. Cima's U.S. Patent No. 5,607,697, for "Taste Masking Microparticles for Oral Dosage Forms," describes a solid dosage form consisting of coated microparticles that disintegrate in the mouth. The microparticle core has a pharmaceutical agent and one or more sweet-tasting compounds having a negative heat of solution selected from mannitol, sorbitol, a mixture of an artificial sweetener and menthol, a mixture of sugar and menthol, and methyl salicylate. The microparticle core is coated, at least partially, with a material that retards dissolution in the mouth and

masks the taste of the pharmaceutical agent. The microparticles are then compressed to form a tablet. Other excipients can also be added to the tablet formulation.

WO 98/46215 for "Rapidly Dissolving Robust Dosage Form," assigned to Cima Labs, is directed to a hard, compressed, fast melt formulation having an active ingredient and a matrix of at least a non-direct compression filler and lubricant. A non-direct compression filler is typically not free-flowing, in contrast to a direct compression (DC grade) filler, and usually requires additionally processing to form free-flowing granules.

Cima also has U.S. patents and international patent applications directed to effervescent dosage forms (U.S. Patent Nos. 5,503,846, 5,223,264, and 5,178,878) and tableting aids for rapidly dissolving dosage forms (U.S. Patent Nos. 5,401,513 and 5,219,574), and rapidly dissolving dosage forms for water soluble drugs (WO 98/14179 for "Taste-Masked Microcapsule Composition and Methods of Manufacture").

Fuisz Technologies, now part of BioVail, markets Flash Dose®, which is a direct compression tablet containing a processed excipient called Shearform®. Shearform® is a cotton candy-like substance of mixed polysaccharides converted to amorphous fibers. U.S. patents describing this technology include U.S. Patent No. 5,871,781 for "Apparatus for Making Rapidly Dissolving Dosage Units;" U.S. Patent No. 5,869,098 for "Fast-Dissolving Comestible Units Formed Under High-Speed/High-Pressure Conditions;" U.S. Patent Nos. 5,866,163, 5,851,553, and 5,622,719, all for "Process and Apparatus for Making Rapidly Dissolving Dosage Units and Product Therefrom;" U.S. Patent No. 5,567,439 for "Delivery of Controlled-Release Systems;" and U.S. Patent No. 5,587,172 for "Process for Forming Quickly Dispersing Comestible Unit and Product Therefrom."

Prographarm markets Flashtab®, which is a fast melt tablet having a disintegrating agent such as carboxymethyl cellulose, a swelling agent such as a modified starch, and a taste-masked active agent. The tablets have an oral disintegration time of under one minute (U.S. Patent No. 5,464,632).

R.P. Scherer markets Zydis®, which is a freeze-dried tablet having an oral dissolution time of 2 to 5 seconds. Lyophilized tablets are costly to manufacture and difficult to package because of the tablets sensitivity to moisture and temperature. U.S. Patent No. 4,642,903 (R.P. Scherer Corp.) refers to a fast melt dosage formulation prepared by dispersing a gas throughout a solution or suspension to be freeze-dried.

U.S. Patent No. 5,188,825 (R.P. Scherer Corp.) refers to freeze-dried dosage forms prepared by bonding or complexing a water-soluble active agent to or with an ion exchange resin to form a substantially water insoluble complex, which is then mixed with an appropriate carrier and freeze dried. U.S. Patent No. 5,631,023 (R. P. Scherer Corp.) refers to freeze-dried drug dosage forms made by adding xanthan gum to a suspension of gelatin and active agent. U.S. Patent No. 5,827,541 (R.P. Scherer Corp.) discloses a process for preparing solid pharmaceutical dosage forms of hydrophobic substances. The process involves freeze-drying a dispersion containing a hydrophobic active ingredient and a surfactant in a non-aqueous phase and a carrier material in an aqueous phase.

Yamanouchi-Shaklee markets Wowtab®, which is a tablet having a combination of a low moldability and a high moldability saccharide. U.S. Patents covering this technology include U.S. Patent No. 5,576,014 for "Intrabuccally Dissolving Compressed Moldings and Production Process Thereof," and U.S. Patent No. 5,446,464 for "Intrabuccally Disintegrating Preparation and Production Thereof."

Other companies owning rapidly dissolving technology include Janssen Pharmaceutica. U.S. patents assigned to Janssen describe rapidly dissolving tablets having two polypeptide (or gelatin) components and a bulking agent, wherein the two components have a net charge of the same sign, and the first component is more soluble in aqueous solution than the second component. *See* U.S. Patent No. 5,807,576 for "Rapidly Dissolving Tablet;" U.S. Patent No. 5,635,210 for "Method of Making a Rapidly Dissolving Tablet;" U.S. Patent No. 5,595,761 for "Particulate Support Matrix for Making a Rapidly Dissolving Tablet;" U.S. Patent No. 5,587,180 for "Process for Making a Particulate Support Matrix for Making a Rapidly Dissolving Tablet;" and U.S. Patent No. 5,776,491 for "Rapidly Dissolving Dosage Form."

Eurand America, Inc. has U.S. patents directed to a rapidly dissolving effervescent composition having a mixture of sodium bicarbonate, citric acid, and ethylcellulose (U.S. Patent Nos. 5,639,475 and 5,709,886).

L.A.B. Pharmaceutical Research owns U.S. patents directed to effervescent-based rapidly dissolving formulations having an effervescent couple of an effervescent acid and an effervescent base (U.S. Patent Nos. 5,807,578 and 5,807,577).

Schering Corporation has technology relating to buccal tablets having an active agent, an excipient (which can be a surfactant) or at least one of sucrose, lactose, or

sorbitol, and either magnesium stearate or sodium dodecyl sulfate (U.S. Patent Nos. 5,112,616 and 5,073,374).

Laboratoire L. LaFon owns technology directed to conventional dosage forms made by lyophilization of an oil-in-water emulsion in which at least one of the two phases contains a surfactant (U.S. Patent No. 4,616,047). For this type of formulation, the active ingredient is maintained in a frozen suspension state and is tableted without micronization or compression, as such processes could damage the active agent.

Takeda Chemicals Inc., Ltd. owns technology directed to a method of making a fast dissolving tablet in which an active agent and a moistened, soluble carbohydrate are compression molded into a tablet, followed by drying of the tablets.

None of the described prior art teaches an immediate release dosage form in which a poorly soluble active ingredient is in a nanoparticulate form. This is significant because the prior art immediate release formulations do not address the problems associated with the bioavailability of poorly soluble drugs. While prior art immediate release dosage forms may provide rapid presentation of a drug, frequently there is an undesirable lag in the onset of therapeutic action because of the poor solubility and associated slow dissolution rate of the drug. Thus, while prior art immediate release dosage forms may exhibit rapid disintegration of the drug carrier matrix, this does not result in rapid dissolution and absorption of the poorly soluble drug contained within the dosage form.

C. Background Regarding Controlled Release Compositions

Controlled release refers to the release of an agent such as a drug from a composition or dosage form in which the agent is released according to a desired profile over an extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic or diagnostic response as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations. For

example, in the treatment of chronic pain, controlled release formulations are often highly preferred over conventional short-acting formulations.

Controlled release pharmaceutical compositions and dosage forms are designed to improve the delivery profile of agents, such as drugs, medicaments, active agents, diagnostic agents, or any substance to be internally administered to an animal, including humans. A controlled release composition is typically used to improve the effects of administered substances by optimizing the kinetics of delivery, thereby increasing bioavailability, convenience, and patient compliance, as well as minimizing side effects associated with inappropriate immediate release rates such as a high initial release rate and, if undesired, uneven blood or tissue levels.

Prior art teachings of the preparation and use of compositions providing for controlled release of an active compound provide various methods of extending the release of a drug following administration.

Exemplary controlled release formulations known in the art include specially coated pellets, microparticles, implants, tablets, minitabs, and capsules in which a controlled release of a drug is brought about, for example, through selective breakdown of the coating of the preparation, through release through the coating, through compounding with a special matrix to affect the release of a drug, or through a combination of these techniques. Some controlled release formulations provide for pulsatile release of a single dose of an active compound at predetermined periods after administration.

U.S. Patent No. 5,110,605 to Acharya et al. refers to a calcium polycarbophil-alginate controlled release composition. U.S. Patent No. 5,215,758 to Krishnamurthy et al. refers to a controlled release suppository composition of sodium alginate and calcium salt. U.S. Patent No. 5,811,388 to Friend et al. refers to a solid alginate-based formulation including alginate, a water-swellable polymer, and a digestible hydrocarbon derivative for providing controlled release of orally administered compounds.

WO 91/13612 refers to the sustained release of pharmaceuticals using compositions in which the drug is complexed with an ion-exchange resin. The specific ion-exchange resin described in this published patent application is AMBERLITE IRP 69®, a sodium polystyrene sulphonate resin.

U.S. Patent No. 5,811,425 to Woods et al. refers to injectable depot forms of controlled release drugs made by forming microencapsule matrices of the drug in biodegradable polymers, liposomes, or microemulsions compatible with body tissues. U.S. Patent No. 5,811,422 to Lam et al. refers to controlled release compositions obtained by coupling a class of drugs to biodegradable polymers, such as polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, etc.

U.S. Patent No. 5,811,404 to De Frees et al. refers to the use of liposomes having prolonged circulation half-lives to provide for the sustained release of drug compositions.

Finally, WO 00/18374, for "Controlled Release Nanoparticulate Compositions," describes controlled release formulations comprising nanoparticulate active agents.

* * * *

There is a need in the art for compositions of poorly soluble drugs having a combination of immediate release and controlled release characteristics. The present invention satisfies this need.

SUMMARY OF THE INVENTION

This invention is directed to the surprising and unexpected discovery of formulations of poorly soluble active agents having a combination of immediate active agent release and controlled active agent release characteristics. The formulations comprise a combination of very small active agent particles, *i.e.*, nanoparticulate active agent particles, in combination with larger active agent particles, *i.e.*, micronized active agent particles, which enable obtaining the simultaneous presentation of immediate-release (IR) and controlled-release (CR) active agent components.

The nanoparticulate active agent particles, representing the IR component, afford rapid *in vivo* dissolution, owing to their small size and attendant large specific surface. Alternatively, micronized active agent particles, representing the CR component, afford slower *in vivo* dissolution, owing to a comparatively large particle size and small attendant specific surface.

IR and CR components representing a wide range of *in vivo* dissolution rates (and hence, *in vivo* input rates for absorption) can be engineered through precise control

of active agent particle size. Thus, the compositions can comprise a mixture of nanoparticulate active agent particles, wherein each population of particles has a defined size correlating with a precise release rate, and the compositions can comprise a mixture of microparticulate active agent particles, wherein each population of particles has a defined size correlating with a precise release rate.

The compositions of the invention are highly unexpected, particularly since the controlled delivery of active agents has traditionally been achieved through employment of rate-controlling membranes, swellable and erodible polymers, and ion-exchange resins, rather than solely through the particle size of the active agent component of the dosage form.

In another aspect of the invention there is provided a method of preparing formulations having a combination of IR and CR characteristics. The method comprises: (1) forming a composition comprising particles of at least one nanoparticulate active agent to be administered and at least one surface stabilizer adsorbed onto the surface of the nanoparticulate active agent particles; (2), adding at least one microparticulate active agent, which can be the same or different from the active agent of (1), and (3) forming a dosage form of the mixture of (1) and (2) for administration. Additional pharmaceutically acceptable excipients can also be added to the composition for administration.

Yet another aspect of the present invention provides a method of treating a mammal, including a human, with a composition of the invention.

It is to be understood that both the foregoing general description and the following brief description of the figures and detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: Shows a simulation, using a mathematical model, of pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing an active agent having a single defined particle size;

FIGURE 2: Shows a simulation, using a mathematical model, of pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing mixtures of different sizes of particles; and

FIGURE 3: Shows a simulation, using a mathematical model, of pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing mixtures of different sizes of particles.

DETAILED DESCRIPTION OF THE INVENTION

A. Compositions

This invention is directed to the surprising and unexpected discovery of new compositions exhibiting a combination of IR and CR characteristics. The compositions do not require the presence of an additional ingredient, such as a rate controlling polymer or membrane, a swellable or erodible polymer, or ion-exchange resin, to obtain the CR characteristics. The IR and CR characteristics are obtained using precisely calibrated particle sizes for the one or more active agents. Smaller particle sizes result in IR profiles and larger particle sizes result in CR profiles.

The compositions of the invention comprise: (1) particles of at least one poorly soluble nanoparticulate active agent; (2) at least one surface stabilizer adsorbed onto the surface of the nanoparticulate active agent particles; and (3) at least one poorly soluble microparticulate active agent, which can be the same as or different from the active agent of (1). As taught in the '684 patent, the surface stabilizer functions to stabilize the nanoparticulate active agent by preventing agglomeration and particle size growth.

Methods of making nanoparticulate active agent compositions, which can comprise mechanical grinding, precipitation, homogenization, or any other suitable size reduction process, are known in the art and are described in, for example, the '684 patent and other prior art references disclosed in the "Background of the Invention."

The nanoparticulate and microparticulate active agent particles can be in a crystalline form, semi-crystalline form, amorphous form, semi-amorphous form, or a combination thereof.

The compositions can be formulated for administration to humans and animals via any conventional means, including but not limited to orally, rectally, parenterally

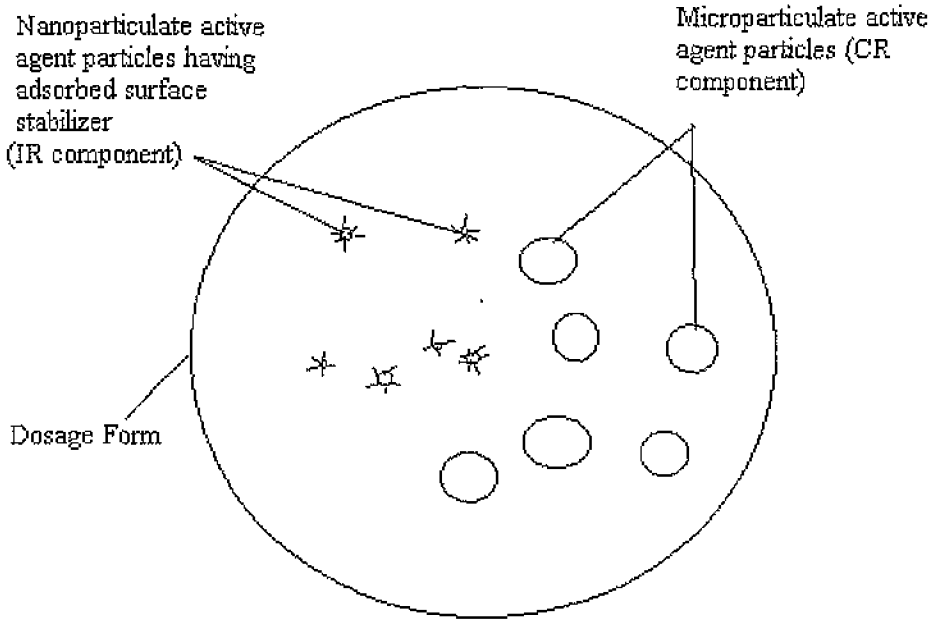
(intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (powders, ointments or drops), ocularly, aurally, or as a buccal or nasal spray.

The present invention also encompasses the compositions of the invention formulated together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection, oral administration in solid or liquid form, rectal or topical administration, ocular or aural administration, and the like.

For oral dosage forms, the IR component results in rapid dissolution of the poorly soluble active agent in the oral cavity as a result of the nanoparticulate size of the drug. Further, the opportunity for buccal absorption of the poorly soluble active ingredient is enhanced with the present invention. Yet another advantage of the nanoparticulate IR component is that the use of nanoparticulate active agent particles eliminates or minimizes the feeling of grittiness found with prior art IR oral formulations of poorly soluble active agents.

One advantage typically associated with IR dosage forms is a reduction of the time lag between administration of a dose and the physical presentation of the active ingredient. This lag time is usually associated with the break up of the dosage form and the distribution of the active ingredient thereafter. Another advantage of oral IR dosage forms is that the rapid presentation of the active agent in the mouth upon administration may facilitate buccal absorption of the active ingredient directly into the blood stream, thus reducing the first pass effect of the liver on the overall bioavailability of active ingredient from a unit dose. This second advantage is dramatically enhanced for the IR formulations of the invention, as the nanoparticulate size of the active agent enables rapid dissolution in the oral cavity.

It is expected that the CR component of the compositions provides effective blood levels of an incorporated active agent in a patient for an extended period of time. As used herein, "controlled release" means the release of an active agent such as a drug from a composition or dosage form in which the agent is released according to a desired profile over an extended period of time, such as from about 2 to about 24 hours or longer. Release over a longer time period is also contemplated as a "controlled release" dosage form of the present invention. An exemplary formulation is graphically illustrated below:



1. Solid Dosage Forms

In a first embodiment of the invention, both of the IR and CR components are incorporated in a solid, rapidly disintegrating or "waterless tablet" matrix intended for oral administration.

In a second embodiment of the invention, the IR and CR components are combined in a pharmaceutically acceptable tablet intended for oral administration.

In a third embodiment of the invention, the IR and CR components are combined in a pharmaceutically acceptable hard gelatin capsule intended for oral administration.

In a fourth embodiment of the invention, the IR and CR components are combined in a pharmaceutically acceptable soft gelatin capsule intended for oral administration. One variation of this dosage form comprises solubilized drug and microparticulate drug particles, in which the solubilized drug functions as the IR component and the microparticulate drug particles function as the CR component of the dosage form. This variation differs from the other dosage forms described herein in that it does not require the presence of "particulate" nanoparticulate drug particles.

In a fifth embodiment of the invention, the IR and CR components are combined in a pharmaceutically acceptable lozenge or troche intended for oral administration.

In a sixth embodiment of the invention, the IR and CR components are combined in a pharmaceutically acceptable sachet, powder, or "sprinkle" intended for oral administration.

2. Other Dosage Forms

Other suitable dosage forms include, but are not limited to, suppositories for rectal or intravaginally use; injectables, including injectables for intravenous, intramuscular, or subcutaneous administration; aerosols for pulmonary or nasal administration; buccal dosage forms; dosage forms for local application, such as powders, ointments, or drops; ocular and aural dosage forms, and dosage forms for intracisternal and intraperitoneal administration.

The IR and CR compositions of the invention can be combined in any pharmaceutically acceptable dosage form, which is not limited to those specifically described above.

3. Poorly Soluble Active Agent

The compositions of the invention comprise at least one poorly soluble therapeutic agent, diagnostic agent, or other active agent. A therapeutic agent can be a drug or pharmaceutical and a diagnostic agent is typically a contrast agent, such as an x-ray contrast agent, or any other type of diagnostic material.

The invention can be practised with a wide variety of poorly soluble drugs or diagnostic agents. The drug or diagnostic agent is preferably present in an essentially pure form, is poorly soluble, and is dispersible in at least one liquid medium. By "poorly soluble" it is meant that the drug or diagnostic agent has a solubility in a liquid dispersion medium of less than about 30 mg/ml, preferably less than about 10 mg/ml, and more preferably less than about 1 mg/ml. Such a liquid dispersion medium can be, for example, water, aqueous salt solutions, oils such as safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol.

The poorly soluble active agent can be selected from a variety of known classes of drugs or diagnostic agents, including, for example, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including

penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (e.g., hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines.

Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. A nutraceutical or dietary supplement, also known as phytochemicals or functional foods, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body. Exemplary nutraceuticals or dietary supplements include, but are not limited to, folic acid, fatty acids (*e.g.*, DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (*e.g.*, iso-leucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

The active agents are commercially available and/or can be prepared by techniques known in the art.

The poorly soluble active ingredient may be present in any amount which is sufficient to elicit a therapeutic effect and, where applicable, may be present either substantially in the form of one optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers.

4. Surface Stabilizers

Useful surface stabilizers, which are known in the art and described, for example, in the '684 patent, are believed to include those which physically adhere to the surface of the active agent but do not chemically bond to or interact with the active agent. The surface stabilizer is adsorbed on the surface of the nanoparticulate active agent in an amount sufficient to maintain an effective average particle size of less than about 1000 nm for the active agent. Furthermore, the individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. Two or more surface stabilizers can be employed in the compositions and methods of the invention.

Suitable surface stabilizers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred surface stabilizers include nonionic and ionic surfactants, including anionic and cationic surfactants.

Representative examples of surface stabilizers include gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation,

Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), dialkylesters of sodium sulfosuccinic acid (*e.g.*, Aerosol OT®, which is a dioctyl ester of sodium sulfosuccinic acid (American Cyanamid)); Duponol P®, which is a sodium lauryl sulfate (DuPont); Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2C(O)N(CH_3)$-$CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, such as Plasdone S630, PEG-derivatized phospholipids, PEG-derivatized cholesterol, PEG-derivatized cholesterol derivatives, PEG-derivatized vitamin A, PEG-derivatized vitamin E, and the like.

Other useful surface stabilizers include sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or a combination thereof.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide,

myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic*

Surfactants: Physical Chemistry (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Particularly preferred nonpolymeric primary stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium

chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

5. Particle Size

The IR characteristics of the dosage form are obtained by utilizing at least one nanoparticulate active agent having an effective average particle size of less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, or less than about 50 nm.

The CR characteristics of the dosage form are obtained by utilizing at least one microparticulate active agent having an effective average particle size of greater than about 1 micron and less than about 100 microns, less than about 90 microns, less than about 80 microns, less than about 70 microns, less than about 60 microns, less than about 50 microns, less than about 40 microns, less than about 30 microns, less than about 20 microns, less than about 10 microns, less than about 9 microns, less than about

8 microns, less than about 7 microns, less than about 6 microns, less than about 5 microns, less than about 4 microns, less than about 3 microns, or less than about 2 microns.

The compositions can comprise multiple populations of nanoparticulate active agent particles, wherein each population of particles has a defined size correlating with a precise release rate, *i.e.* a first population having an effective average particle size of less than about 1 micron, a second population having an effective average particle size of less than about 800 nm, a third population having an effective average particle size of less than about 500 nm, a fourth population having an effective average particle size of less than about 50 nm, *etc.*, with each population corresponding to a specific release rate.

Similarly, the compositions can comprise multiple populations of microparticulate active agent particles, wherein each population of particles has a defined size correlating with a precise release rate, *i.e.* a first population having an effective average particle size of less than about 100 microns, a second population having an effective average particle size of less than about 60 microns, a third population having an effective average particle size of less than about 40 microns, a fourth population having an effective average particle size of less than about 20 microns, *etc.*, with each population corresponding to a specific release rate.

Each population of particles in the composition, both nanoparticulate and microparticulate, exhibits a baseline resolution of at least 50%, 60%, 70%, 80%, or 90%. This means that the heterogeneous population is characterized by a multi-modal particle size distribution, with a minimum baseline resolution of 50% relative to two adjacent peaks. 50% baseline resolution is defined as half the distance from the baseline of the distribution to the average height of two adjacent peaks.

The baseline resolution of at least 50% distinguishes the claimed invention from a conventional microparticulate composition having a mixture of particle sizes, as in such a conventional composition the particle sizes are randomly distributed and do not have a baseline resolution of at least 50% for two or more particle sizes.

As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation

field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

By "an effective average particle size of less than about 1000 nm" it is meant that at least 50% of the active agent particles have an average particle size of less than about 1000 nm, when measured by the above techniques. Similarly, by "an effective average particle size of less than about 100 microns, it is meant that at least 50% of the active agent particles have an average particle size of less than about 100 microns, when measured by the above techniques. Preferably, at least 70% of the particles have an average particle size of less than the effective average, more preferably at least about 90% of the particles have an average particle size of less than the effective average.

6. Other Pharmaceutical Excipients

Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (SMCC).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200; talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or

mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the acid component of the effervescent couple may be present.

7. Quantities of Nanoparticulate Active Agent, Surface Stabilizer, and Microparticulate Active Agent

The relative amount of at least one nanoparticulate active agent, one or more surface stabilizers, and at least one microparticulate active agent can vary widely. The optimal amount of the surface stabilizers can depend, for example, upon the particular active agent selected, the hydrophilic lipophilic balance (HLB), melting point, and water solubility of the surface stabilizer, and the surface tension of water solutions of the stabilizer, *etc.*

The concentration of at least one nanoparticulate active agent can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined weight of the at least one active agent and at least one surface stabilizer, not including other excipients.

The concentration of at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5% to about 99.9%, and from about 10% to about 99.5%, by weight, based on the total combined dry weight of at least one active agent and at least one surface stabilizer, not including other excipients.

The concentration of the microparticulate active agent can vary from about 5% to about 85%, by weight, based on the total combined weight of the nanoparticulate

active agent, surface stabilizer, and microparticulate active agent, not including other excipients.

B. Methods of Making Compositions of the Invention

In another aspect of the invention there is provided a method of preparing formulations having combined CR and IR characteristics. The method comprises: (1) forming a nanoparticulate composition comprising at least one nanoparticulate active agent to be administered and at least one surface stabilizer; (2) adding at least one microparticulate active agent, which is the same or different from the nanoparticulate active agent of (1), and (3) forming a suitable dosage form of the composition for administration. Pharmaceutically acceptable excipients can also be added to the composition for administration.

1. Methods of Making Nanoparticulate Compositions

Methods of making nanoparticulate compositions, which can comprise mechanical grinding, precipitation, homogenization, or any other suitable size reduction process, are known in the art and are described in, for example, the '684 patent.

Methods of making nanoparticulate compositions are also described in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331, for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883, for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932, for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133, for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270, for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583, for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

a. Milling to obtain Nanoparticulate Active Agent Dispersions

Milling of aqueous active agent dispersions to obtain a nanoparticulate dispersion comprises dispersing at least one active agent in a liquid dispersion medium in which the active agent is poorly soluble. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion medium of less than about 30 mg/ml, preferably less than about 10 mg/ml, and more preferably less than about 1 mg/ml. Such a liquid dispersion medium can be, for example, water, aqueous salt solutions, oils such as safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol.

This is followed by applying mechanical means in the presence of grinding media to reduce the particle size of the active agent to the desired effective average particle size. The active agent particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the active agent particles may be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the active agent/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode. The resultant nanoparticulate active agent dispersion can be used directly in formulating a dosage form, or the dispersion can be formulated into a powder followed by dosage formulation.

b. Precipitation to Obtain Nanoparticulate Active Agent Compositions

Another method of forming the desired nanoparticulate composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving the poorly water-soluble active agent in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer to form a solution; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means. The resultant nanoparticulate active agent dispersion can be used directly in formulating a dosage

form, or the dispersion can be formulated into a powder followed by dosage formulation.

c. Homogenization to Obtain Nanoparticulate Active Agent Compositions

Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Such a method comprises dispersing active agent particles in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of the active agent particles to the desired effective average particle size. The active agent particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the active agent particles can be contacted with one or more surface stabilizers either before or after particle size reduction. It is preferred, however, to disperse the active agent particles in the liquid dispersion medium in the presence of the at least one surface stabilizer as an aid to wetting of the active agent particles. Other compounds, such as a diluent, can be added to the active agent/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode. The resultant nanoparticulate active agent dispersion can be used directly in formulating a dosage form, or the dispersion can be formulated into a powder followed by dosage formulation.

2. Dosage Formulation

Methods of making oral, injectable, transdermal, aerosol, buccal, topical, ocular, aural, *etc.* pharmaceutical formulations are known in the art, and such methods can be employed in the present invention.

In one embodiment of the invention, nanoparticulate active agent particles having at least one surface stabilizer adsorbed on to the surface of the particles can be incorporated into a dry powder matrix (*e.g.*, through spray drying, spray granulation, or a related pharmaceutically acceptable drying process), and combined with bulk micronized active agent particles by dry blending or a similar mixing process.

In a second embodiment of the invention, nanoparticulate active agent particles can be incorporated into a dry powder matrix (*e.g.*, through spray drying, spray

granulation, or a related pharmaceutically acceptable drying process). Separately, micronized active agent particles can be incorporated into a dry powder matrix using a similar approach, and the resulting matrices can then be combined by dry blending or a similar mixing process.

In a third embodiment of the invention, micronized active agent particles can be prepared by dry milling (*e.g.*, jet milling or pin milling).

In a fourth embodiment of the invention, micronized active agent particles can be prepared by wet milling, similar to the approach employed in the preparation of nanoparticulate active agent particles described in the '684 patent.

In an fifth embodiment of the invention, micronized active agent particles can be employed as the substrate (or a portion thereof) in a spray granulation, rotogranulation, spray coating, or related pharmaceutical process, upon which nanoparticulate active agent particles can be dispersed or deposited to form an outer layer. This particular approach facilitates the release of nanoparticulate active agent particles from the outer layer of the matrix upon exposure to biological fluids, followed by exposure and subsequent dissolution of micronized active agent particles.

In a sixth embodiment of the invention, micronized active agent particles can be employed as the substrate (or a portion thereof) in a high-shear granulation or related pharmaceutical wet-mixing process, upon which nanoparticulate active agent particles can be applied in the form of a granulating fluid. Upon drying, this particular approach enable nanoparticulate active agent particles and micronized active agent particles to be homogeneously distributed in the resulting solid matrix.

In a seventh embodiment of the invention, nanoparticulate active agent particles and micronized active agent particles can exist in the form of a dry powder or powder blend suitable for incorporation into a solid, rapidly disintegrating or "waterless tablet" matrix, the latter being attained upon compression of the dry powder or powder blend using a tablet press or similar pharmaceutically acceptable compression machine.

Exemplary spray drying, lyophilization, granulation, and tableting methods are described below.

a. <u>Spray Drying of Nanoparticulate Dispersions</u>

Dosage forms of nanoparticulate dispersions can be prepared by drying the nanoparticulate formulation following size reduction. A preferred drying method is

spray drying. The spray drying process is used to obtain a nanoparticulate powder following the size reduction process used to transform the active agent into nanoparticulate sized particles.

In an exemplary spray drying process, the nanoparticulate active agent suspension is fed to an atomizer using a peristaltic pump and atomized into a fine spray of droplets. The spray is contacted with hot air in the drying chamber resulting in the evaporation of moisture from the droplets. The resulting spray is passed into a cyclone where the powder is separated and collected. The nanoparticulate dispersion can be spray-dried in the presence or absence of excipients to give the spray-dried intermediate powder.

The powder can be formulated, for example, into a tablet, suppository, or other solid dosage form, or the powder can be formulated into an aerosol for nasal or pulmonary administration. The powder can also be reconstituted into a liquid, and used, for example, for injectable, ocular, ear, or oral dosage forms.

b. Lyophilization

Solid dose forms of nanoparticulate dispersions can also be prepared by lyophilizing the nanoparticulate formulation following size reduction. Suitable lyophilization conditions include, for example, those described in EP 0,363,365 (McNeil-PPC Inc.), U.S. Patent No. 4,178,695 (A. Erbeia), and U.S. Patent No. 5,384,124 (Farmalyoc), all of which are incorporated herein by reference. Typically, the nanoparticulate dispersion is placed in a suitable vessel and frozen to a temperature of between about -5°C to about -100°C. The frozen dispersion is then subjected to reduced pressure for a period of up to about 48 hours. The combination of parameters such as temperature, pressure, dispersion medium, and batch size will impact the time required for the lyophilization process. Under conditions of reduced temperature and pressure, the frozen solvent is removed by sublimation yielding a solid, porous, IR solid dosage form having the active ingredient distributed throughout.

The powder can be formulated, for example, into a tablet, suppository, or other solid dosage form, or the powder can be formulated into an aerosol for nasal or pulmonary administration. The powder can also be reconstituted into a liquid, and used, for example, for injectable, ocular, ear, or oral dosage forms.

c. Granulation

Alternatively, a solid oral dosage form of the invention can be prepared by granulating in a fluidized bed an admixture comprising a nanoparticulate dispersion of active agent and at least one surface stabilizer with a solution of at least one pharmaceutically acceptable water-soluble or water-dispersible excipient, to form a granulate. This is followed by tableting of the granulate to form a solid dosage form.

d. Tableting

The dosage formulations of the invention can be in the form of tablets. Preparation of such tablets can be by pharmaceutical compression or molding techniques known in the art. The tablets of the invention may take any appropriate shape, such as discoid, round, oval, oblong, cylindrical, triangular, hexagonal, and the like.

Powders for tableting can be formulated into tablets by any method known in the art. Suitable methods include, but are not limited to, milling, fluid bed granulation, dry granulation, direct compression, spheronization, spray congealing, and spray-dying. Detailed descriptions of tableting methods are provided in *Remington: The Science and Practice of Pharmacy*, 19th ed. Vol. 11 (1995) (Mack Publishing Co., Pennsylvania); and *Remington's Pharmaceutical Sciences*, Chapter 89, pp. 1633-1658 (Mach Publishing Company, 1990), both of which are specifically incorporated by reference.

The tablets may be coated or uncoated. If coated they may be sugar-coated (to cover objectionable tastes or odors and to protect against oxidation) or film coated (a thin film of water soluble matter for similar purposes).

C. Administration of the Compositions of the Invention

The present invention provides a method of treating a mammal, including a human, requiring the rapid availability of at least one poorly soluble active ingredient in combination with controlled release of the same or a different poorly soluble active ingredient. The administered compositions of the invention rapidly release an incorporated active agent resulting in fast onset of activity, and simultaneously slowly release the same or a different active agent for a prolonged pharmacological effect.

In general, the compositions of the invention will be administered to a mammalian subject in need thereof using a level of drug or active agent that is sufficient

to provide the desired physiological effect. The mammalian subject may be a domestic animal or pet but preferably is a human subject. The level of drug or active agent needed to give the desired physiological result is readily determined by one of ordinary skill in the art by referring to standard texts, such as *Goodman and Gillman* and the *Physician's Desk Reference*.

* * * * *

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available documents are specifically incorporated into this patent application by reference.

Example 1

The purpose of this example was to simulate, using a mathematical model, pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing an active agent having a single defined particle size.

The software used for the simulation was MicroMath PKAnalyst for Windows, version 1.1, MicroMath, Inc. The following assumptions were made: the active agent conforms to a 2-compartment (central and peripheral compartments) pharmacokinetic model with 1st-order absorption and 1st-order elimination from the central compartment.

D/V (dose/volume) = 5000;

$K_a > 1.000\ h^{-1}$ (rate constant corresponding to the rate of dissolution);

$K_e = 0.50\ h^{-1}$ (elimination rate constant);

$K_{12} = 0.25\ h^{-1}$ (constant representing the rate of diffusion from the central compartment to the peripheral compartment); and

$K_{21} = 0.125\ h^{-1}$ (constant representing the rate of diffusion from the peripheral compartment to the central compartment).

Four samples were designed, (S) small particles, (MS) medium small particles, (ML) medium large particles, and (L) particles, having the following dissolution rate constants:

dissolution rate constant for small (S) particles	$= 1.000\ h^{-1}$
dissolution rate constant for medium small (MS) particles	$= 0.500\ h^{-1}$
dissolution rate constant for medium large (ML) particles	$= 0.250\ h^{-1}$

dissolution rate constant for large (L) particles $= 0.125\ h^{-1}$

The results of the simulation are shown in Figure 1.

The small particle population (S) showed rapid onset of activity, peaking at a plasma concentration level of about 2100 mg/mL at a little over 1 hour following administration, with plasma levels of over 250 mg/mL several minutes following administration. However, this sample also exhibited the lowest plasma levels at 12 hours after administration.

In contrast, the large particle population (L) showed slow onset of activity, peaking at a plasma concentration level of a little over 500 mg/mL at about 2 hours after administration. However, this sample also exhibited the highest plasma levels at 12 hours after administration.

The results of the simulation demonstrate that small particles dissolve faster than larger particles, but that they also decay more rapidly. As a consequence, larger drug particles provide the longest blood plasma levels, although these same particles exhibit slow dissolution.

Example 2

The purpose of this example was to simulate, using a mathematical model, pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing mixtures of different sizes of particles.

The assumptions described in Example 1 are applicable to Example 2.

Simulated pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing 50:50 mixtures of small (S) particles plus medium-small (MS), medium-large (ML), or large (L) particles of an active pharmaceutical ingredient are shown in Figure 2.

The results show, in particular, that the mixture of (S) small and (L) large particles exhibits a significantly greater maximum mean plasma concentration (almost 1000 mg/mL) as compared to the (L) large particles administered in Example 1, and the formulation also exhibits prolonged blood plasma levels, in contrast to the to the (S) small particles administered in Example 1.

Example 3

The purpose of this example was to simulate, using a mathematical model, pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing mixtures of different sizes of particles.

The assumptions described in Example 1 are applicable to Example 3.

Simulated pharmacokinetic profiles following single oral doses of a pharmaceutical formulation containing 25:75 mixtures of small (S) plus medium-small (MS), medium-large (ML), or large (L) particles of an active pharmaceutical ingredient are shown in Figure 3.

The results show, in particular, that the mixture of (S) small and (L) large particles exhibits a significantly greater maximum mean plasma concentration (almost 900 mg/mL) as compared to the (L) large particles administered in Example 1, and the formulation also exhibits prolonged blood plasma levels, in contrast to the to the (S) small particles administered in Example 1.

* * * *

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WE CLAIM:

1. A composition comprising:

(a) particles of at least one poorly soluble active agent having an effective average particle size of less than about 1 micron;

(b) at least one surface stabilizer adsorbed onto the surface of the nanoparticulate active agent particles; and

(c) at least one micronized active agent, which is either the same as or different from the active agent of (a), and having an effective average particle size of greater than about 1 micron and less than about 100 microns.

2. The composition of claim 1, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, and less than about 50 nm.

3. The composition of claim 1 or 2, wherein the effective average particle size of the microparticulate active agent particles is greater than about 1 micron and less than the size selected from the group consisting of less than about 90 microns, less than about 80 microns, less than about 70 microns, less than about 60 microns, less than about 50 microns, less than about 40 microns, less than about 30 microns, less than about 20 microns, less than about 10 microns, less than about 9 microns, less than about 8 microns, less than about 7 microns, less than about 6 microns, less than about 5 microns, less than about 4 microns, less than about 3 microns, and less than about 2 microns.

4. The composition of any of claims 1-3 comprising more than one population of nanoparticulate active agent particles, wherein each population of particles has an effective average particle size which is less than about 1 micron.

5. The composition of any of claims 1-4 comprising more than one population of microparticulate active agent particles, wherein each population of particles has an effective average particle size which is greater than about 1 micron and less than about 100 microns.

6. The composition of any of claims 1-5, wherein the concentration of the nanoparticulate active agent is from about 99.5% to about 0.001%, based upon the total weight of the nanoparticulate active agent and the surface stabilizer.

7. The composition of any of claims 1-6, wherein the concentration of the nanoparticulate active agent is from about 95% to about 0.1% (w/w), based upon the total weight of the nanoparticulate active agent and the surface stabilizer.

8. The composition of any of claims 1-7, wherein the concentration of the nanoparticulate active agent is from about 90% to about 0.5% (w/w), based upon the total weight of the nanoparticulate active agent and the surface stabilizer.

9. The composition of any of claims 1-8, wherein the concentration of the surface stabilizer is from about 0.5% to about 99.999% (w/w), based upon the total weight of the nanoparticulate active agent and the surface stabilizer.

10. The composition of any of claims 1-9, wherein the concentration of the surface stabilizer is from about 5% to about 99.9% (w/w), based upon the total weight of the nanoparticulate active agent and the surface stabilizer.

11. The composition of any of claims 1-10, wherein the concentration of the surface stabilizer is from about 10% to about 99.5% (w/w), based upon the total weight of the nanoparticulate active agent and the surface stabilizer.

12. The composition of any of claims 1-11, wherein the concentration of the microparticulate agent is from about 5% to about 85%, based upon the total weight of the microparticulate active agent, nanoparticulate active agent, and surface stabilizer.

13. The composition of any of claims 1-12 formulated into a solid, rapidly disintegrating, "waterless tablet" matrix.

14. The composition of any of claims 1-12 formulated into a pharmaceutically acceptable tablet.

15. The composition of any of claims 1-12 formulated into a pharmaceutically acceptable hard gelatin capsule.

16. The composition of any of claims 1-12 formulated into a pharmaceutically acceptable soft gelatin capsule.

17. The composition of claim 16, wherein the composition comprises solubilized active agent in place of the nanoparticulate active agent particles.

18. The composition of any of claims 1-12 formulated into a pharmaceutically acceptable lozenge or troche.

19. The composition of any of claims 1-12 formulated into a pharmaceutically acceptable sachet, powder, or "sprinkle".

20. The composition of any of claims 1-19 formulated into a dosage form for oral, rectal, intravaginal, injectable, pulmonary, nasal, buccal, topical, local, intracisternal, intraperitoneal, ocular, aural, buccal spray, or nasal spray administration.

21. The composition of any of claims 1-20, wherein the formulation is made utilizing at least one method selected from the group consisting of spray drying, spray granulation, fluid bed granulation, high shear granulation, fluid bed drying, lyophilization, tableting, jet milling, pin milling, wet milling, rotogranulation, and spray coating.

22. The composition of any of claims 1-21, wherein the nanoparticulate and microparticulate active agents are selected from the group consisting of proteins,

peptides, nucleotides, anti-obesity drugs, nutraceuticals, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

23. The composition of any of claims 1-22, wherein the at least one surface stabilizer is selected from the group consisting of a nonionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, and an ionic surface stabilizer.

24. The composition of any of claims 1-23, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, stearic acid esters and salts, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, a charged phospholipid, dimyristoyl phophatidyl glycerol, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate,

alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, triblock copolymers of the structure: -(-PEO)--(-PBO-)--(-PEO-)-, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl β-D-thioglucoside, n-hexyl β-D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl β-D-thioglucopyranoside, lysozyme, a PEG derivatized phospholipid, PEG derivatized cholesterol, a PEG derivatized cholesterol derivative, PEG derivatized vitamin A, PEG derivatized vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

25. The composition of any of claims 1-23, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

26. The composition of any of claims 1-23, wherein the at least one surface stabilizer is selected from the group consisting of cationic lipids, benzalkonium chloride, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride, lauryl dimethyl $(ethenoxy)_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14})

dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride; N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, cationic guar, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, poly (2-methacryloxyethyltrimethylammonium bromide) (S1001), poly(N-vinylpyrrolidone/2-dimethylaminoethyl methacrylate) di methylsulphate quarternary (S1002), and poly(2-methylacryloxyamidopropyltrimethylammonium chloride) (S1004).

27. The composition of any of claims 1-26, comprising two or more surface stabilizers.

28. The composition of any of claims 1-27, comprising sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or a combination thereof, as surface stabilizers.

29. A method of preparing a formulation comprising:

(a) combining (i) particles of at least one nanoparticulate poorly soluble active agent and at least one surface stabilizer adsorbed to the surface thereof, wherein the nanoparticulate active agent has an effective average particle size of less than about 1000 nm, and (ii) at least one microparticulate active agent having an effective average particle size of greater than about 1 micron and less than about 10 microns; and

(b) forming a suitable dosage formulation.

30. The method of claims 29, wherein the microparticulate active agent particles are prepared by dry milling.

31. The method of claim 29 or 30, wherein the microparticulate, nanoparticulate, or both active agent particles are prepared by wet milling.

32. The method of any of claims 29-31, wherein the nanoparticulate active agent particles having at least one surface stabilizer adsorbed onto the surface of the particles are incorporated into a dry powder matrix by spray drying, spray granulation, lyophilization, or a related pharmaceutically acceptable drying process, and then combined with bulk micronized active agent particles by dry blending or a similar mixing process.

33. The method of any of claim 29-32, wherein:

(a) the nanoparticulate active agent particles having at least one surface stabilizer adsorbed on to the surface of the particles are incorporated into a dry powder matrix by spray drying, spray granulation, lyophilization, or a related pharmaceutically acceptable drying process;

(b) the micronized active agent particles are incorporated into a dry powder matrix by spray drying, spray granulation, lyophilization, or a related pharmaceutically acceptable drying process; and

(c) the resulting matrices from (a) and (b) are combined by dry blending or a similar mixing process.

34. The method of any of claims 29-31, wherein the microparticulate active agent particles are coated with the nanoparticulate active agent/surface stabilizer particles.

35. The method of claim 34, wherein the coating is accomplished by a method selected from the group consisting of spray granulation, rotogranulation, spray coating, or a related pharmaceutical process.

36. The method of any of claims 29-31, wherein the microparticulate active agent particles are employed as a substrate in a high-shear granulation or related pharmaceutical wet-mixing process, upon which nanoparticulate active agent/surface stabilizer particles are applied in the form of a granulating fluid, wherein upon drying the nanoparticulate active agent particles and microparticulate active agent particles are homogeneously distributed in the resulting solid matrix.

37. The method of any of claims 29-36, wherein the nanoparticulate active agent/surface stabilizer particles and microparticulate active agent particles are formulated into a dry powder or powder blend for incorporation into a solid, rapidly disintegrating matrix, followed by compressing the dry powder or powder blend using a tablet press or similar pharmaceutically acceptable compression machine to form tablets.

38. Use of the composition of claim 1 for making a pharmaceutical which is useful in treating a mammal.

FIGURE 1

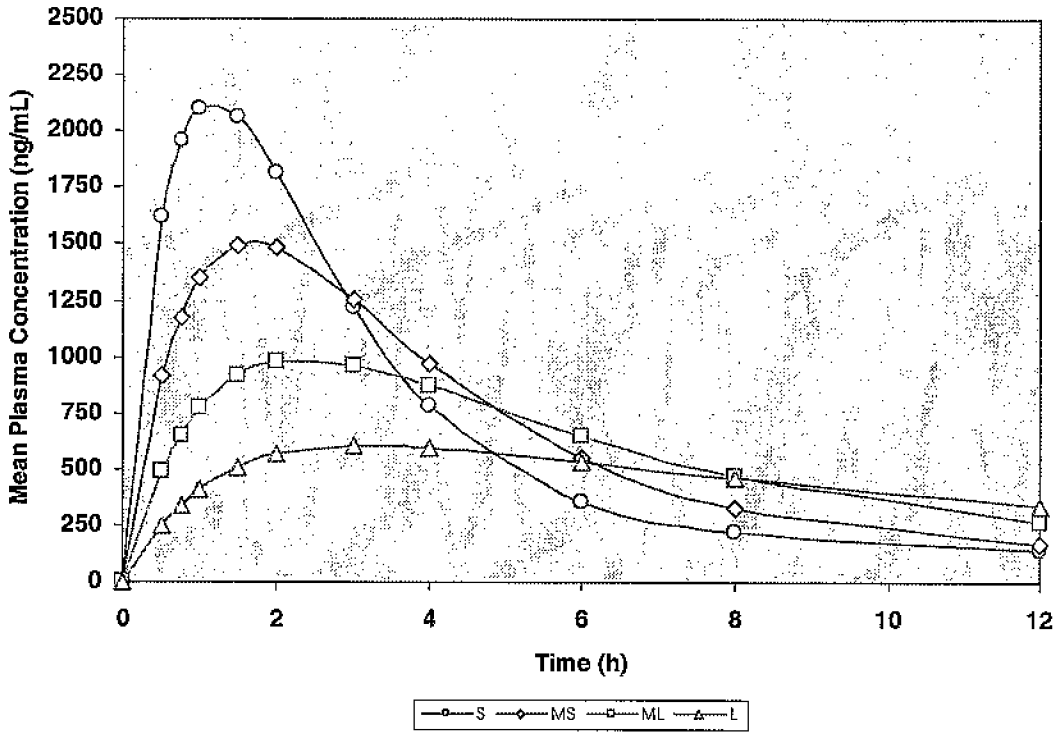


FIGURE 2

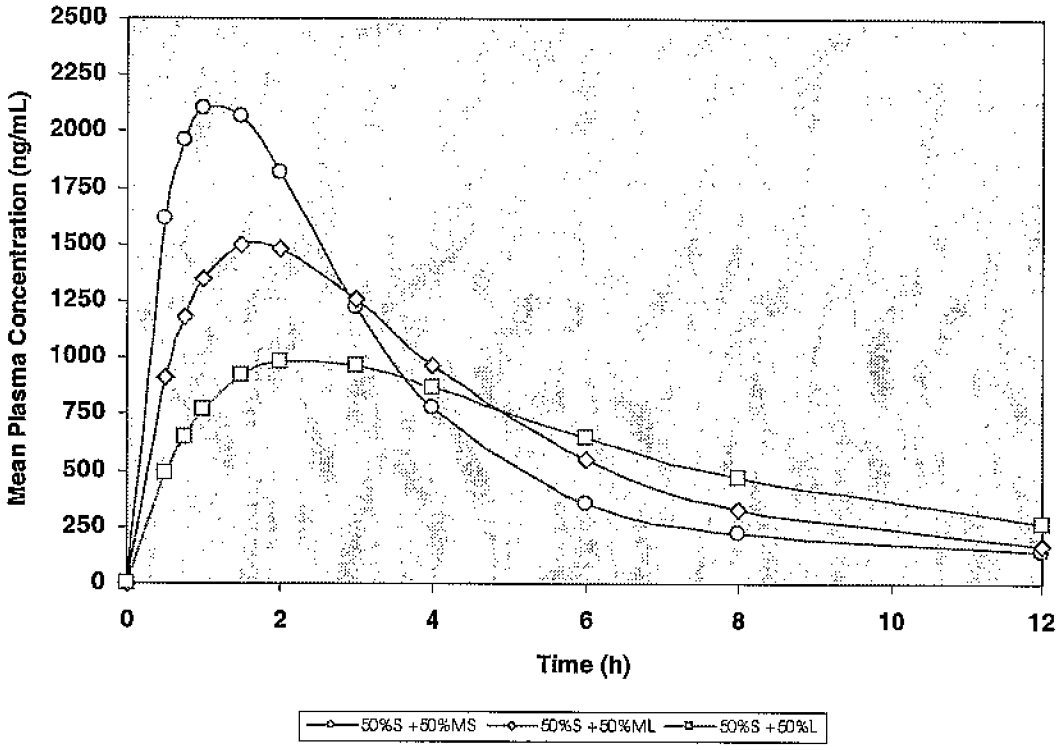
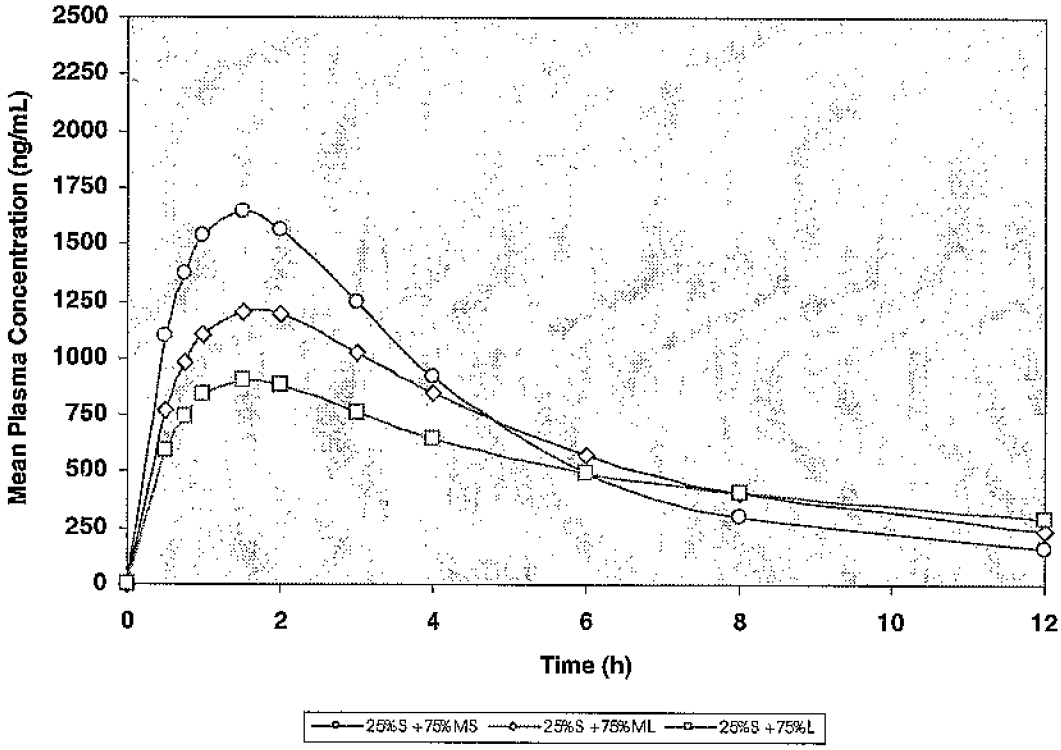


FIGURE 3



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(54)【発明の名称】表面安定剤としてペプチドを有するナノ粒子組成物

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